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CALCIUM AND IODINE METABOLISM IN THYROID DISEASE

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A disturbance of the calcium balance has been found in thyroid disease.[1] Apparently there is a relationship between the calcium and iodine intake, the normal function of the thyroid gland and the development of goiter.[2] Consequently, we became interested in determining any existing correlation between the total calcium and iodine metabolism and thyroid disease in man.

For at least a century calcium has been considered a factor in the production of goiter. As early as 1837 McClelland [3] reported this belief. The iodine deficiency theory of goiter, which has been accepted by

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1. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism: III. The Effects of the Thyroid Hormone and Thyroid Disease, J. Clin. Investigation **7**:97, 1929.

2. (*a*) Tanabe, H.: Experimenteller Beitrag zur Aetiologie des Kropfes, Beitr. z. path. Anat. u. z. allg. Path. **73**:415, 1925. (*b*) Hellwig, C. A.: Iodine Deficiency and Goiter: Influence of a Diet Poor in Iodine on the Thyroid Gland in White Rats, Arch. Path. **11**:709 (May) 1931; Experimental Goiter: Functional, Chemical and Histologic Studies, ibid. **19**:364 (March) 1935. (*c*) Thompson, J.: Influence of the Intake of Calcium on the Thyroid Gland of the Albino Rat, ibid. **16**:211 (Aug.) 1933; The Influence of Calcium and Iodine on Growing Rats, Endocrinology **17**:537, 1933. (*d*) Klein, J.: The Effect of Calcium on the Storage of Colloid in the Thyroid Gland, Ann. Int. Med. **7**:1080, 1934; The Correlation of Mineral Metabolism and the Vegetative Nervous System in Thyroid Disease, ibid. **8**:798, 1935.

3. McClelland, J. W.: On the Connection Between Goiter and Cretinism: Their Nature and Causes; Some Inquiries in the Province of Kemaon Relative to Geology and Other Branches of Natural Science, Including an Inquiry into the Causes of Goiter, Calcutta, 1835, Dublin J. M. Sc. **11**:295, 1837.

many, was advocated by Maffoni [4] in 1846, by Prevost [5] in 1849 and by Chatin [6] in 1852.

Reviews of the earlier literature on calcium metabolism in thyroid disease have been presented.[7] However, until Aub and his associates [1] reported their systematic studies in 1929, the evidence for a disturbance of calcium metabolism remained inconclusive. The true nature of this disturbance remains unknown. Hansman and Wilson [8] did not accept Aub's [1] thesis that thyroxine has a direct catabolic effect on the calcium deposits in bone. Aub and his associates [9] stated that they did not consider the increased excretion of calcium as assisting in the excretion of acid metabolites, nor did they find it influenced by the administration of viosterol.[10]

The literature on iodine feeding, on the absorption of iodine and on the food, blood, thyroid and urinary iodine in health and in thyroid disease, with substantiatory and supplemental data, has already been presented by Curtis and his associates.[11] The studies of the total iodine

4. Maffoni, A. C.: Brevi cenni sullo stato sanitario del piemonte con proposta di alcuni mezzi per giungere a migliorarlo, Atti d. Accad. di med. di Torino **2**:453, 1846.

5. Prevost, J. L., quoted by Orr and Leitch.[18]

6. Chatin, A.: Recherche de l'iode dans l'air, les eaux, le sol et les produits alimentaires des alpes de la France et du Piédmont, Compt. rend. Acad. d. sc. **33**:529, 1851; **34**:14 and 51, 1852.

7. Golden, R., and Abbott, H.: The Relation of the Thyroid, the Adrenals and the Islands of Langerhans to Malacic Diseases of Bone, Am. J. Roentgenol. **30**:641, 1933. Aub and others.[1]

8. Hansman, F. S., and Wilson, F. H.: Calcium and Phosphorus Metabolism in Diseases of the Thyroparathyroid Apparatus: I. Calcium, Phosphorus and Total Metabolism in Hyperthyroidism and the Part Played by the Parathyroid Glands, M. J. Australia **1**:37, 1934.

9. Albright, F.; Bauer, W., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: VIII. The Influence of the Thyroid Gland and the Parathyroid Hormone upon the Total Acid-Base Metabolism, J. Clin. Investigation **10**:187, 1931.

10. Tibbetts, D. M.; McLean, R., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: XX. The High Calcium Excretion in Exophthalmic Goiter Is Not Due to Vitamine D Deficiency, J. Clin. Investigation **11**:1273, 1932.

11. (*a*) Phillips, F. J.; Erf, O., and Curtis, G. M.: The Effects of Prolonged Increased Iodine Feeding, Ohio J. Sc. **35**:286, 1935. (*b*) Cole, V. V.; Dunn, R. H., and Curtis, G. M.: The Intrapulmonic Absorption of Iodine, J. Pharmacol. & Exper. Therap. **53**:327, 1935. (*c*) Cole, V. V.; Curtis, G. M., and Bone, M. L.: The Iodine Content of Hospital Foods, J. Am. Dietet. A. **10**:200, 1934. (*d*) Davis, C. B.; Curtis, G. M., and Cole, V. V.: Blood Iodine Studies: II. The Normal Iodine Content of Human Blood, J. Lab. & Clin. Med. **19**:818, 1934. (*e*) Curtis,

(Footnote continued on next page)

metabolism of normal subjects and of patients with thyroid disease reported to date have been few.[12] This literature was reviewed recently.[13] At present the chief reason for the inability of investigators to interpret the interrelationship of calcium and iodine metabolism to the function of the thyroid gland is a lack of firmly established facts concerning the total metabolism of either calcium or iodine.

Recently, the experimental evidence of Zondek and Reiter,[14] Tanabe,[2a] Abelin,[15] Hellwig,[2b] Thompson,[2c] Klein [2d] and of others has been considered indicative of an interrelationship between calcium and iodine in the production of goiter. However, Remington and Levine [16] stated that varying the calcium content and the calcium-phosphorus ratio of the goitrogenic diet does not significantly affect the degree of goiter produced in the rat.

This report is concerned with the presentation of the results of an investigation of the calcium and iodine balance made pretherapeutically of one patient with hypothyroidism, two normal subjects and two patients with exophthalmic goiter.

G. M.; Cole, V. V., and Phillips, F. J.: The Blood Iodine in Thyroid Disease, West. J. Surg. **42**:435, 1934. (*f*) Curtis, G. M.: Iodine Metabolism in Toxic Goiter, J. Med. **15**:294, 1934. (*g*) Curtis, G. M., and Phillips, F. J.: The Urinary Excretion of Iodine: I. The Loss of Iodine in the Urine Following Thyroidectomy, J. Clin. Investigation **13**:777, 1934. (*h*) Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of the Iodine Content of Human Blood, J. A. M. A. **101**:901 (Sept. 16) 1933. (*i*) Curtis, G. M.; Barron, L. E., and Phillips, F. J.: Blood Iodine Studies: V. Blood Iodine After Total Thyroidectomy in Man, J. Lab. & Clin. Med. **20**:813, 1935. (*j*) Matthews, N. L.; Cole, V. V., and Curtis, G. M.: The Urinary Excretion of Iodine: II. The Normal Urinary Iodine in Central Ohio, to be published. (*k*) Cole, V. V., and Curtis, G. M.: Cyclic Variations in Urinary Excretion of Iodine in Women, Proc. Soc. Exper. Biol. & Med. **31**:29, 1933.

12. (*a*) von Fellenberg, T.: Untersuchungen über den Jodstoffwechsel: I. Versuche mit physiologischen Jodmengen beim Erwachsenen, Biochem. Ztschr. **142**: 246, 1923; (*b*) Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods, Ergebn. d. Physiol. **25**:176, 1926. (*c*) Scheffer, L.: Ueber die Jodbilanz normaler Menschen, Biochem. Ztschr. **11**:259, 1933; Jodstoffwechsel bei Schilddrüsenkranken, Klin. Wchnschr. **12**:1285, 1933; Jodstoffwechsel bei Hyperthyreosen, ibid. **13**:1570, 1934.

13. Cole, V. V., and Curtis, G. M.: Human Iodine Balance, J. Nutrition **10**: 493, 1935.

14. Zondek, H., and Reiter, I., quoted by Marine, D.: The Pathogenesis and Prevention of Simple and Endemic Goiter, J. A. M. A. **104**:2334 (June 29) 1935.

15. Abelin, I.: Schilddrüse und Mineralstoffwechsel: Einfluss des Dinatriumphosphats und der Calciumsalze auf die Wirkung der Schilddrüsensubstanzen, Biochem. Ztschr. **199**:72, 1928.

16. Remington, R. E., and Levine, H.: Personal communication to the authors.

EXPERIMENTAL METHODS

The principles underlying the choice of diet in the investigation of mineral metabolism have been discussed by many.[17] The constant diet which we used, selected and begun by each subject two or three days prior to this investigation, was of a low calcium and sufficient iodine content, adequate in other respects and as attractive as possible. One patient with exophthalmic goiter was maintained on a high calcium intake. All foods known to be rich in iodine were excluded.[11c] The normal iodine requirements for man are not definitely known. The minimum daily requirement for a man has been stated as 45 micrograms.[18] Eggenberger[19] stated that from 40 to 80 micrograms probably covers the daily need for iodine. Our usual hospital diet has been considered of sufficient iodine content.[11c] The diets of patients G. L. and E. K. were probably at the lower limits of sufficiency. The caloric value was calculated as basal plus 20 to 30 per cent. The daily intake of protein was 1 Gm. per kilogram. The intake of salt and fluid as well as the acid-base values of the diet were maintained within a narrow range. This diet had a low fat content. The five subjects remained at rest in bed under special care throughout the period of study. They did not lose weight. Only one research worker and one assistant were permitted to give the patients food and water and to take care of the urine and feces. The loss of iodine through perspiration and expiration was minimized by the rest in bed and by careful adjustment of the temperature of the room.

This investigation was divided into periods of three days each. Equal weights of food were taken for consumption and for analysis. The food of each period for analysis was dried in an evaporating dish, ground, thoroughly mixed and weighed. Urine was collected in twenty-four hour specimens, preserved in an icebox, measured and diluted to 2,000 cc. Analyses were made on the mixed three day specimen. The feces for each period were marked off by carmine in the usual manner. These were dried, ground in a grinding mill, well mixed, weighed and preserved for analysis.

LABORATORY METHODS

Various methods have been described for the determination of the calcium content of urine, food and feces. These methods have the disadvantage of requiring

17. Bauer, W.; Albright, F., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: II. The Calcium Excretion of Normal Individuals on a Low Calcium Diet, J. Clin. Investigation **7**:75, 1929. Lusk, G.: The Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928. Barker, L. F.; Hoskins, R. G., and Mosenthal, H. O.: Endocrinology and Metabolism, ed. 1, New York, D. Appleton & Co., 1922. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, Physiol. Rev. **8**:283, 1928. Sherman, H. C.: The Chemistry of Food and Nutrition, ed. 4, New York, The Macmillan Company, 1933. Hansman and Wilson.[8]

18. Orr, J. B., and Leitch, I.: Iodine in Nutrition, Medical Research Council, Special Report Series, no. 123, London, His Majesty's Stationery Office, 1929.

19. Eggenberger, H., cited by Marine, D.: The Pathogenesis and Prevention of Simple or Endemic Goiter, J. A. M. A. **104**:2334 (June 29) 1935.

expensive apparatus and of being laborious and time consuming [20] or of incompletely oxidizing the organic matter.[21] In this laboratory we have devised a perchloric acid method for the determination of the calcium content. Perchloric acid, when concentrated and hot, is a more powerful oxidizing agent than sodium persulfate, which is used in the Shohl-Pedley method,[21a] or of sulfuric acid, which is often used for wet ashing.[22] Bumping and spattering are much less likely to occur than when sulfuric acid is used. The oxidation is smoother and more rapid and complete. The whole procedure is carried out in one specially made centrifuge tube.[23] Qualitative and not quantitative transfer and filtration are avoided.

A sample, containing the amount of calcium suitable for the Clark-Collip [24] method of determining the calcium content of the blood, is first oxidized with perchloric acid. Precipitation, washing of the precipitate and titration with potassium permanganate are then carried out according to the principles set forth by McCrudden,[20a] Shohl,[25] Shohl and Pedley [21a] and Clark and Collip.[24] The method as applied to urine is as follows:

1. To 5 or 10 cc. of urine in a 75 cc. specially made pyrex centrifuge tube add 2 cc. of perchloric acid (60 per cent) per five cubic centimeters of urine.

2. Gently evaporate the contents of the tube for a few minutes over a microburner or an ordinary burner until the heavy white fumes of perchloric acid arise. One or two drops of caprylic alcohol may be used to prevent foaming.

3. When the contents of the tube turn brown, add concentrated nitric acid, drop by drop, until the solution becomes clear and colorless or slightly yellow.

4. When all the organic matter has been oxidized, allow the contents of the tube to cool somewhat and then dissolve the perchlorates with 30 cc. of water.

5. Add 10 cc. of normal oxalic acid.

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20. (*a*) McCrudden, F. H.: The Determination of Calcium in the Presence of Magnesium and Phosphates: The Determination of Calcium in Urine, J. Biol. Chem. **10**:187, 1911-1912. (*b*) Van Slyke, D. D., and Sendroy, J., Jr.: Gasometric Determination of Oxalic Acid and Calcium, and Its Application to Serum Analysis, ibid. **84**:217, 1929.

21. (*a*) Shohl, A. T., and Pedley, F. G.: A Rapid and Accurate Method for Calcium in Urine, J. Biol. Chem. **50**:537, 1922. (*b*) Stearns, G.: A Rapid Method for the Preparation of Fecal Digests Suitable for Use in Nitrogen and Mineral Analyses, J. Lab. & Clin. Med. **14**:954, 1929.

22. Neumann, A.: Eine Veraschungsmethode (Säuregemisch-Veraschung) und vereinfachte Bestimmungen von Eisen, Phosphorsäure, Salzsäure und anderen Aschenbestandteilen unter Benutzung dieser Säuregemisch-Veraschung, Ztschr. f. physiol. Chem. **37**:115, 1902. Stearns.[21b]

23. The pyrex centrifuge tube is conical, with a capacity of 75 cc., and sufficiently narrow at the bottom (2 or 3 mm., inner diameter) to hold together the precipitate and permit none to escape when the fluid is decanted. It has a tip of thick glass. This tube may be purchased from the Kauffman-Lattimer Co., Columbus, Ohio.

24. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

25. Shohl, A. T.: The Effect of Hydrogen Ion Concentration upon the Determination of Calcium, J. Biol. Chem. **50**:527, 1922.

6. Adjust the p_H (p_H 4 to 5.6) of the solution with concentrated ammonium hydroxide so as just to exceed the end-point, and complete the adjustment with 10 per cent hydrochloric acid until a pink color is obtained, using 1 drop of methyl red (0.2 in 50 per cent alcohol) as the indicator.

7. Let stand overnight. Centrifugate for ten minutes at 1,500 revolutions per minute and wash three times with ammonium hydroxide (0.5 per cent) by the Clark-Collip method [24] of decantation.

8. Redissolve the calcium oxalate precipitate in 10 cc. of normal sulfuric acid. Heat to 70 or 80 C.

9. Titrate with hundredth normal potassium permanganate and calculate.

This method, with slight modifications, was applied also to food and feces.

In order to test the accuracy of this method several experiments (table 1) were carried out. No effort was made to obtain the highest degree of accuracy;

TABLE 1.—*Data on the Accuracy of the Method Employed*

Theoretical Solutions					Recovery of Added Calcium				
Calcium Taken,* Mg.	Uric Acid Added, Mg.	Perchloric Acid (60%), Cc.	Calcium Found, Mg.	Deviation, Mg.	Urine,† Cc.	Calcium Added, Mg.	Calcium Obtained, Mg.	Added Calcium Recovered, Mg.	Deviation, Mg.
0.00	0	4	0.00	.....	10	0.00	0.53	....	....
0.00	10	4	0.00	.....	10	0.00	Lost	....	....
0.88	0	4	0.90	+0.02	10	0.00	0.54	....	....
0.88	0	4	0.89	+0.01	10	0.88	1.44	0.90	+0.02
0.88	10	4	0.89	+0.01	10	0.88	1.46	0.92	+0.04
0.88	10	4	0.90	+0.02	10	0.88	1.45	0.91	+0.03

* The theoretical solution of calcium used in this experiment was made by dissolving 0.22 Gm. of calcium carbonate (calcite for standardizing, obtained from the General Chemical Co., code no. 1791; obtained through the Kauffman-Lattimer Co., Columbus, Ohio) in 10 cc. of calcium-free concentrated hydrochloric acid plus double-distilled water and diluted to 1 liter with double-distilled water. The uric acid (10 per cent) was calcium free.

† The samples were obtained from the same specimen of urine.

the results represent those obtainable by an analyst of moderate experience. These results (table 1) compare favorably with those obtained by the usual wet ashing method.

The calcium content of the blood was determined by the Clark and Collip [24] method. The phosphorus content was determined by the King [26] method. The iodine content of the blood, urine, water, food, sweat and feces of normal subjects was determined [13] by the Phillips and Curtis [27] method and that of patients with thyroid disease [28] by the McCullagh [29] method.

All analyses were made in duplicate and were repeated when adequate checks were not obtained.

26. King, E. J.: The Colorimetric Determination of Phosphorus, Biochem. J. **26**:292, 1932.

27. Phillips, F. J., and Curtis, G. M.: Blood Iodine Studies: IV. The Clinical Determination of Iodine in Blood, Urine and Feces, Am. J. Clin. Path. **4**:346, 1934.

28. Dr. Versa V. Cole gave permission for us to use these data.

29. McCullagh, D. R.: A New Method for the Determination of Iodine, J. Biol. Chem. **107**:35, 1934.

Two normal subjects were studied. The calcium values were comparable to those obtained by other investigators,[30] whose data have been reviewed.[17]

NORMAL CONTROLS

E. S., a white taxicab driver, single, aged 27, volunteered for this experiment. He had always enjoyed good health. Clinical examination showed no abnormalities. He had previously received no iodine or iodized salt.

Laboratory examination revealed negative Wassermann and Kahn reactions of the blood. Moderate anemia was present. The leukocyte and differential counts were normal. The urine was normal. The basal metabolic rate on Dec. 3, 1933, was minus 1, with the basal pulse rate 59, the temperature 97.6 F., the respiratory rate 12, the blood pressure 100 systolic and 70 diastolic and the weight 121 pounds (55 Kg.).

Comment.—The calcium and phosphorus contents of the blood (table 2) averaged 10.5 and 4.1 mg., respectively, which are normal. The fecal excretion of calcium was greater than the urinary excretion. This subject, with a low calcium intake of 696 mg. per three day period, showed a continuous but normal negative calcium balance. The total excretion of calcium was 153 per cent of the intake.

The blood iodine averaged 13.4 micrograms per hundred cubic centimeters, which is normal. The urinary excretion of iodine was greater than the fecal excretion. This subject, with a sufficient iodine intake, 468 micrograms per three day period, was in continuous positive iodine balance. The urinary and fecal excretion of iodine was about 50 per cent of the intake of iodine.[19] These data are presented in table 2.

G. L., a white woman of 31, a worker in a shoe factory, volunteered as a normal subject for this investigation. Her general health was good at the time of this study. Clinical examination showed no abnormalities. She had received no iodine or iodized salt previous to hospitalization. Laboratory examination revealed that the blood and urine were normal. The Wassermann and Kahn reactions of the blood were negative. The Graham-Cole test for hepatic function gave negative results. The basal metabolic rate on Feb. 4, 1934, was minus 10, with the basal pulse rate 69, the temperature 98.2 F., the respiratory rate 15, the blood pressure 110 systolic and 70 diastolic and the weight 108 pounds (49 Kg.).

30. Sherman, H. C.: Calcium Requirements of Maintenance in Man, J. Biol. Chem. **44**:21, 1920. Rose, M. S.: Experiments on the Utilization of the Calcium of Carrots by Man, ibid. **41**:349, 1920. Bogert, L. J., and Kirkpatrick, E. E.: Studies in Inorganic Metabolism: II. The Effects of Acid Forming and Base Forming Diets upon Calcium Metabolism, ibid. **54**:375, 1922. Sherman, H. C.; Wheeler, L., and Yates, A. B.: Experiments on the Nutritive Value of Maize Protein and on the Phosphorus and Calcium Requirements of Healthy Women, ibid. **34**:383, 1918. Sherman, H. C.; Gillett, L. H., and Pope, H. M.: Monthly Metabolism of Nitrogen, Phosphorus and Calcium in Healthy Women, ibid. **34**: 373, 1918. Sherman, H. C.; Winters, J. C., and Phillips, V.: Efficiency of Oat Protein in Adult Human Nutrition, ibid. **34**:53, 1919.

TABLE 2.—*Data for E. S., a Normal White Man* *

Period	Date When Started	Weight, Kg.	Calcium					Iodine					Blood				Basal Metabolic Rate, %
			Output			Intake, Gm.	Balance, Gm.	Output			Intake, Mcgm.	Balance, Mcgm.	Date	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Iodine, Mcgm. per 100 Cc.	
			Urine, Gm.	Feces, Gm.	Total, Gm.			Urine, Mcgm.†	Feces, Mcgm.	Total, Mcgm.							
1	12/ 6/33	55.0	0.104	1.206	1.310	0.657	—0.653	154	114	268	469	+201	12/ 3/33	....	...	....	— 1
													12/ 6/33	....	...	....	— 6
2	12/ 9/33	53.5	0.404	0.524	0.928	0.713	—0.215	137	58	195	505	+310	12/ 7/33	....	...	11.9	
													12/10/33	10.4	4.2		
3	12/12/33	53.0	0.572	0.664	1.236	0.670	—0.566	161	89	250	469	+219	12/12/33	....	...	....	—15
4	12/15/33	....	0.315	0.460	0.775	0.725	—0.050	130	93	223	449	+226	12/13/33	10.6	4.4	15.7	
5	12/18/33	....	0.272	0.805	1.077	0.718	—0.359	142	48	190	451	+261	12/20/33	10.5	3.7	12.6	
Average for entire period.....		53.8	0.333	0.732	1.065	0.696	—0.369	145	80	225	468	+243	Average	10.5	4.1	13.4	— 7

* E. S. was 28 years old. He received a diet containing 1,900 calories, with 55 Gm. of protein.

† A microgram equals 0.001 mg. It is frequently called a gamma.

Comment.—The calcium and the phosphorus content of the blood (table 3) averaged 10.1 and 4.6 mg. per hundred cubic centimeters, respectively, which are normal values. The fecal excretion of calcium was greater than the urinary excretion. This subject, with a low calcium intake, 984 mg. per three day period, showed a normal negative calcium balance. The total excretion of calcium was 102 per cent of the intake.

The blood iodine averaged 7.9 micrograms per hundred cubic centimeters, which is a low normal value. The urinary excretion of iodine was greater than the fecal excretion.[13] This subject, with an intake of 168 micrograms of iodine per three day period, showed a continuous positive iodine balance. The urinary and fecal excretion of iodine was 80 per cent of the intake of iodine. These data are presented in table 3.

HYPOTHYROIDISM

E. K., a white housewife aged 38, was mildly myxedematous. She was readmitted to the University Hospital for this investigation after total thyroidectomy for essential hypertension four and a half months previously.

Data concerning the total thyroidectomy are presented elsewhere.[31] In the interval her general health had been good. The blood pressure had returned to its original level of about 210 systolic and 130 diastolic; nevertheless, some symptomatic improvement had been noted. The headaches in the occipital region had largely disappeared. There was evidence of an early stage of myxedema. The patient complained of lethargy and said she always felt cold. There had been a gain in weight. She said she had taken no thyroid medication or iodized salt after the total thyroidectomy.

Physical examination revealed essentially no abnormality, except for the elevated blood pressure. No dependent edema was noted. No objective signs of hypoparathyroidism were disclosed. The blood showed a slight anemia, with a decreased hemoglobin content. On February 13 examination of the blood showed 5,050 leukocytes, with 56 per cent neutrophils, 6 per cent eosinophils, 2 per cent basophils, 18 per cent lymphocytes and 18 per cent monocytes. Urinalysis revealed no abnormality, except for a trace of albumin. The Wassermann and Kahn tests of the blood were negative. After the intravenous injection of phenolsulfonphthalein there was elimination of 40 per cent of the dye at the end of one hour, and of 5 per cent at the end of the second hour. The nonprotein nitrogen content of the blood was 33 mg. per hundred cubic centimeters. An electrocardiogram showed evidence of first degree heart block and suggested myocardial damage. The basal metabolic rate on February 12 was minus 25, with the basal pulse rate 63, the temperature 98 F., the respiratory rate 12, the blood pressure 190 systolic and 130 diastolic and the weight 131 pounds (60 Kg.).

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31. Curtis, G. M.; Barron, L. E., and Matthews, N. L.: The Urinary Excretion of Iodine: II. The Loss of Iodine in the Urine Following Total Thyroidectomy in Man, to be published.

TABLE 3.—*G. L., a Normal White Woman* *

Period	Date When Started	Weight, Kg.	Calcium					Iodine					Blood				Basal Metabolic Rate, %
			Output			Intake, Gm.	Balance, Gm.	Output			Intake, Mcgm.	Balance, Mcgm.	Date	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Iodine, Mcgm. per 100 Cc.	
			Urine, Gm.	Feces, Gm.	Total, Gm.			Urine, Mcgm.	Feces, Mcgm.	Total, Mcgm.							
1	2/ 7/34	50	0.408	0.608	1.010	1.075	+0.059	107	25	132	168	+36	2/ 4/34	....	...	....	−10
2	2/10/34	..	0.366	0.557	0.923	0.884	−0.039	107	19	126	171	+45	2/ 8/34	9.1	4.3	9.0	
3	2/13/34	..	0.378	0.546	0.924	0.962	+0.038	109	29	138	163	+25					
4	2/16/34	..	0.402	0.490	0.892	0.994	+0.102	94	29	123	164	+41	2/19/34	10.9	4.8	7.2	
5	2/19/34	50	0.408	0.857	1.265	1.004	−0.261	101	33	134	173	+39	2/23/34	....	...	7.5	
Average for entire period.....		50	0.392	0.612	1.004	0.984	−0.020	104	27	131	168	+37	Average	10.0	4.6	7.9	−10

* G. L. was a normal white woman aged 31. She received a diet containing 1,500 calories, with 50 Gm. of protein.

Comment.—The calcium content of the blood (table 4) averaged 8.9 mg. per hundred cubic centimeters, which is normal. The urinary excretion of calcium was greater than the fecal excretion. This patient, with a low calcium intake, 377 mg. per three day period, was in continuous negative calcium balance. This balance was less than that of normal subjects with such a low calcium intake. The total excretion of calcium was 153 per cent of the intake.

The value for blood iodine averaged 5.4 micrograms per hundred cubic centimeters, which is below normal. The urinary excretion of iodine was greater than the fecal excretion.[13] This subject, with an iodine intake of 117 micrograms per three day period, was in continuous positive iodine balance. The urinary and fecal excretion of iodine was approximately 80 per cent of the intake of iodine. The value for sweat iodine also was determined for this patient.[13] These data are shown in table 4.

EXOPHTHALMIC GOITER

T. F., a white housewife aged 24, was transferred on April 9, 1934, to the Research Surgical Service for this investigation and for thyroidectomy.

Since November 1932 she had been aware of nervousness, tachycardia, dyspnea, tremor of the upper extremities and emotional and heat instability. She had noted exophthalmos for about one year. She had noted the presence of a goiter for a month. She had received no iodine for at least two months previous to this investigation. Physical examination showed no evidence of disease other than that referable to exophthalmic goiter.

Laboratory investigation revealed the blood and urine to be normal. The Wassermann and Kahn tests of the blood were negative. A roentgenogram of the hands showed no detectable evidence of decalcification. Plummer and Dunlap[32] have presented the reports of patients who showed roentgenologic osteoporosis due to decalcification. The basal metabolic rate on April 2 was plus 61 per cent, with the basal pulse rate 103, the temperature 99 F., the respiratory rate 30, the blood pressure 148 systolic and 84 diastolic and the weight 124 pounds (56 Kg.).

Under hospital management alone this patient showed a remission of the clinical manifestations. There was a fall in the basal metabolic rate over a period of twenty-three days to plus 25 per cent on April 25, with the basal pulse rate 103, the temperature 97.2 F., the respiratory rate 19, the blood pressure 128 systolic and 70 diastolic and the weight 127 pounds (58 Kg.). The investigation was terminated on April 27. Five cubic centimeters of diiodotyrosine (10 mg. of iodine) was then given daily at noon beginning on April 30. This had little further effect on the basal metabolic rate. On May 5 the basal metabolic rate was plus 21 per cent, with the basal pulse rate 98, the temperature 98 F., the respiratory rate 15 and the weight 134 pounds (61 Kg.). Thyroidectomy was accomplished on May 10. Eighty grams of characteristic diffuse hyperplastic goiter was removed. Microscopic examination showed extensive and generalized iodine-induced colloid involution. There was a definite differential involution with a minimal amount of vacuolation. The colloid was thin and granular. There was considerable hyperinvolution. Round cell infiltration was minimal.

32. Plummer, W. A., and Dunlap, H. F.: Cases Showing Osteoporosis Due to Decalcification in Exophthalmic Goiter, Proc. Staff Meet., Mayo Clin. **3**:119, 1928.

TABLE 4.—*Data for E. K., a Woman with Myxedema**

Period	Date When Started	Weight, Kg.	Calcium					Iodine					Blood				
			Output			Intake, Gm.	Balance, Gm.	Output			Intake, Mcgm.	Balance, Mcgm.	Date	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Iodine, Mcgm. per 100 Cc.	Basal Metabolic Rate, %
			Urine, Gm.	Feces, Gm.	Total, Gm.			Urine, Mcgm.	Feces, Mcgm.	Total, Mcgm.							
1	4/11/34	60.5	0.345	0.215	0.560	0.414	−0.146	72	27	99	123	+24	11/22/33	9.0			
													2/12/34	8.4	4.4		
2	4/14/34	60.5	0.324	0.272	0.596	0.340	−0.256	60	30	90	111	+21	4/15/34	9.2	...	6.1	−22
													4/17/34	...	...	6.0	−28
													4/18/34	9.1	4.3	4.2	
Average for entire period.....		60.5	0.335	0.243	0.578	0.377	−0.201	66	29	95	117	+22	Average	8.9	4.4	5.4	−25

* E. K. was a 38 year old housewife. Myxedema had followed total thyroidectomy (Nov. 21, 1933) for essential hypertension. She received a diet containing 1,240 calories, with 50 Gm. of protein.

Comment.—The calcium and the phosphorus content (table 5) averaged 10.3 and 3.9 mg. per hundred cubic centimeters of blood, respectively, which is normal. The fecal excretion of calcium was greater than the urinary excretion. Even with the high calcium intake of 2,455 mg. per three day period, this patient was in *continuous, moderately increased negative balance.* The total excretion of calcium was 144 per cent of the intake of calcium.

The value for blood iodine averaged 26 micrograms per hundred cubic centimeters, which is considerably above normal. The fecal excretion of iodine was greater than the urinary excretion.[13] This patient, with an intake of 466 micrograms of iodine per three day period, was, exclusive of the sweat iodine, in low positive iodine balance. The urinary and fecal excretion of iodine was about 96 per cent of the intake of iodine. The differences in the excretion of iodine by E. S., a normal control, and this patient with hyperthyroidism are largely accounted for by the greater excretion of iodine in the feces of the latter. The value for sweat iodine was determined also for this patient.[13] These data are given in table 5.

R. S., a white housewife aged 24, entered the University Hospital for this investigation and for thyroidectomy on Oct. 30, 1934. She had had nervousness, tachycardia, palpitation, emotional and heat instability, polyphagia, polydypsia and polyuria since April, at which time she first noted exophthalmos. Six weeks before her admission to the hospital she became aware of a goiter. Since that time the size of the goiter had fluctuated considerably, the gland being more prominent during menstruation. The patient had taken a proprietary preparation containing iodine for from two to four weeks previous to this investigation. The physical examination, except for the observations referable to the exophthalmic goiter, revealed no essential abnormality.

Laboratory examination revealed that the blood and urine were normal. The hemoglobin value was slightly decreased. The Wassermann and Kahn tests of the blood were negative. The Scott-Reinhart test for pregnancy was negative. Roentgenograms of the hands showed no detectable evidence of decalcification. The basal metabolic rate on November 5 was plus 81 per cent, with the basal pulse rate 112, the temperature 98.6 F., the respiratory rate 24, the blood pressure 130 systolic and 50 diastolic and the weight 103 pounds (47 Kg.).

With hospital management the patient showed a slight remission of the clinical manifestations. Over a period of seventeen days the basal metabolic rate decreased only slightly (to plus 68 per cent) on November 22, with the basal pulse rate 107, the temperature 98.8 F., the respiratory rate 11, the blood pressure 142 systolic and 68 diastolic and the weight 100 pounds (45 Kg.). The investigation was completed on November 17, and iodine medication (10 mg. daily, given as potassium iodide) was begun immediately. This medication had a marked effect on the basal metabolic rate. On November 25 the basal metabolic rate was plus 38 per cent, with the basal pulse rate 95, the temperature 97.8 F., the respiratory rate 11 and the weight 102 pounds (46 Kg.). Thyroidectomy was accomplished on November 28. Sixty-two grams of characteristic diffuse hyperplastic goiter was removed. Microscopic examination showed a variable iodine-induced colloid involution, some evidence of early nodule formation and extensive lymphocytic infiltration with localized aggregations.

TABLE 5.—*Data for T. F., a Woman with Exophthalmic Goiter* *

			Calcium					Iodine					Blood				
			Output					Output									
Period	Date When Started	Weight, Kg.	Urine, Gm.	Feces, Gm.	Total, Gm.	Intake, Gm.	Balance, Gm.	Urine, Mcgm.	Feces, Mcgm.	Total, Mcgm.	Intake, Mcgm.	Balance, Mcgm.	Date	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Iodine, Mcgm. per 100 Cc.	Basal Metabolic Rate, %
1	4/12/34	57.5	0.651	3.156	3.807	1.996	—1.811	138	282	420	502	+82					
2	4/15/34	....	0.303	2.999	3.302	2.702	—0.600	189	271	460	465	+ 5	4/16/34	....	...	....	+28
3	4/18/34	....	0.474	3.812	4.286	2.748	—1.538	132	293	425	493	+68					
4	4/21/34	....	0.444	2.454	2.898	2.422	—0.476	189	284	473	424	—49	4/23/34	....	...	26	
													4/25/34	10.6	4.4	..	+25
5	4/24/34	57.5	0.348	3.058	3.406	2.348	—1.058	138	272	410	446	+36	5/ 4/34	10.0	3.5		
Average for entire period.....		57.5	0.456	3.096	3.552	2.455	—1.097	157	280	437	466	+29	Average	10.3	3.9	26	+26

* T. F. was 24 years old. She received a diet containing 3,350 calories, with 57 Gm. of protein.

Comment.—The calcium and the phosphorus content (table 6) averaged 10.4 and 4.8 mg. per hundred cubic centimeters of blood, respectively, which is normal. The fecal excretion of calcium was greater than the urinary excretion. This patient, with a low calcium intake, 942 mg. per three day period, was in continuous and greatly increased negative calcium balance. The total excretion of calcium was 314 per cent of the intake.

The value for blood iodine was 22 micrograms per hundred cubic centimeters, which is moderately above normal. The fecal excretion of iodine was greater than the urinary excretion.[13] This patient, with a sufficient iodine intake, 653 micrograms per three day period, was in continuous negative iodine balance. The urinary and fecal excretion of iodine was 117 per cent of the intake of iodine. The value for sweat iodine was determined also for this patient.[13] Table 6 presents these data.

COMMENT

The calcium and the phosphorus content of the blood of all five subjects varied within normal limits. The patient with hypothyroidism showed a higher than normal retention of calcium. In the two normal subjects with a low calcium diet the calcium balance was negative. The two patients with exophthalmic goiter showed an increase in the excretion of calcium. In one the increase was almost entirely by way of the feces. In the other the increase was by way of both the urine and the feces, and this resulted in a continuous negative calcium balance greater than normal. These data are readily appreciated by an inspection of the accompanying chart. They confirm the investigations of Aub and his co-workers [1] on the total calcium metabolism as related to thyroid disease in man and those of Pugsley and Anderson [33] for the rat. Hypotheses as to the cause of this increase in the amount of calcium excreted have been advanced.[34] It is possible that the loss of calcium is due to a combination of factors, the underlying cause of which is the increased utilization of thyroid hormone by the tissues.

The value for blood iodine of the normal subjects averaged 10.7 micrograms per hundred cubic centimeters.[13] For the patient with hypothyroidism the value for blood iodine averaged 5.4 micrograms per hundred cubic centimeters, which is low. The value for blood iodine of the two patients with exophthalmic goiter averaged 24 micrograms per hundred cubic centimeters, which is high. Normal subjects and those with hypothyroidism were in continuous positive iodine balance. The

33. Pugsley, L. I., and Anderson, E.: The Effect of Desiccated Thyroid, Irradiated Ergosterol and Ammonium Chloride on the Excretion of Calcium in Rats, Biochem. J. **28**:754, 1934.

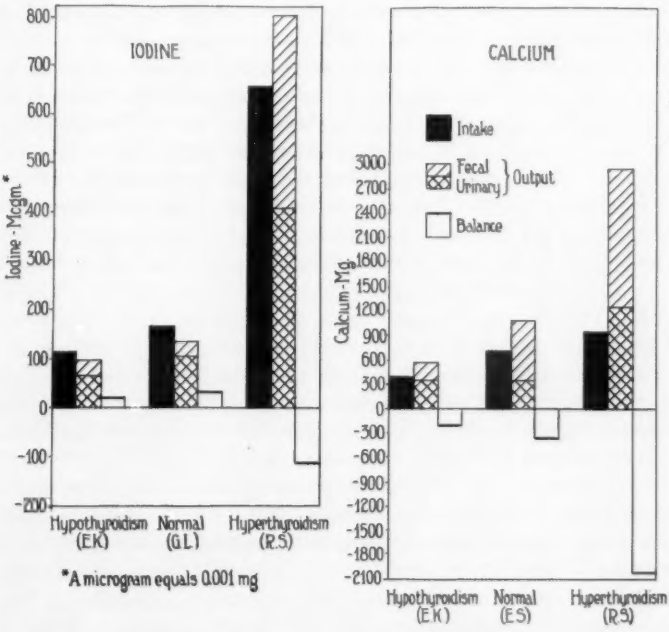
34. Aub, Bauer, Heath and Ropes.[1] Hansman and Wilson.[8] Albright, Bauer and Aub.[9] Tibbetts, McLean and Aub.[10]

TABLE 6.—*Data for R. S., a Woman with Exophthalmic Goiter* *

Period	Date When Started	Weight, Kg.	Calcium					Iodine					Blood				Basal Metabolic Rate, %
			Output			Intake, Gm.	Balance, Gm.	Output			Intake, Mcgm.	Balance, Mcgm.	Date	Serum Calcium, Mg. per 100 Cc.	Serum Phosphorus, Mg. per 100 Cc.	Iodine, Mcgm. per 100 Cc.	
			Urine, Gm.	Feces, Gm.	Total, Gm.			Urine, Mcgm.	Feces, Mcgm.	Total, Mcgm.							
1	11/ 8/34	47.0	1.188	1.641	2.829	0.883	−1.946	204	393	597	495	−102	11/ 6/34	....	...	..	+81
2	11/11/34	48.0	1.059	1.742	2.801	0.943	−1.858	345	135	480	462	− 18	11/ 9/34	....	...	..	+84
													11/19/34	....	...	..	+65
3	11/14/34	46.5	1.506	1.752	3.258	1.000	−2.258	516	699	1,215	1,002	−213	11/22/34	....	...	..	+68
													11/24/34	10.4	4.8		
													11/25/34	....	...	22	
Average for entire period.....		47.0	1.251	1.712	2.963	0.942	−2.021	355	409	764	653	−111	Average	10.4	4.8	22	+75

* R. S. was 24 years old. She received a diet containing 3,800 calories, with 50 Gm. of protein.

urinary loss of iodine was greater than the fecal excretion. In one patient with exophthalmic goiter the iodine balance was continuously negative. In the other patient also it was less than that of the two normal controls. In both the increased fecal excretion of iodine was greater than the increased urinary excretion of iodine, thus showing a difference from normal subjects and those with hypothyroidism. These results are presented in the accompanying chart. They are in agreement with the findings of Fellenberg [12a, b] for normal subjects, of



A comparison of the average calcium and iodine values for a patient with hypothyroidism (E. K.) and a patient with hyperthyroidism (R. S.) with those for normal controls (G. L. and E. S.).

Scheffer [35] for normal subjects and for patients with exophthalmic goiter and of Schittenhelm and Eisler [36] for an adult with myxedema.

These results show that the thyroid gland is a principal organ in maintaining the iodine content of the blood at an average normal level.

35. Scheffer, L.: Ueber die Rolle des Jods bei der Entstehung von Schilddrüsenkrankheiten, Schweiz. med. Wchnschr. **64**:969, 1934. Scheffer.[12c]

36. Schittenhelm, A., and Eisler, B.: Der Jodstoffwechsel des Myxödematösen, Ztschr. f. d. ges. exper. Med. **80**:589, 1932.

From investigations made subsequent to total thyroidectomy on E. K. and on others [37] it is obvious that the true picture of iodine metabolism cannot be determined by a study of the blood iodine alone. Such study determines principally the amount of mobile iodine. It does not indicate the destiny of the iodine, and it reveals nothing of its origin, storage, utilization or excretion.

Fellenberg [12b] pointed out that the storage of iodine is of two types: first, a temporary, readily available storage, which he located in the thyroid gland, and, second, a more permanent, less easily mobilizable storage, which, he theorized, may be located in the thyroid gland, the blood or possibly in the liver or elsewhere. His researches, however, had not extended this far. The results noted in the case of E. K. and also in other cases [37] suggest that the extrathyroid tissues contain a readily available supply of iodine, as indicated by the immediate and great rise in the urinary excretion of iodine subsequent to total thyroidectomy. They suggest also that the more permanent storage of iodine is extrathyroid, since the characteristic slow mobilization and elimination of the element continue even after the total removal of the thyroid gland. It may be that this iodine is located in the cellular protein.

Abelin [38] produced a thyroxine-like substance by artificially iodizing protein. This had a calorigenic effect on totally thyroidectomized rats. He concluded that there is an extrathyroid substance in the organism which has a similar physiologic action, a substance which he called homothyroxine. It is possible that this is one of the factors which maintains the basal metabolism in a totally thyroidectomized patient and prevents it from decreasing more than 30 or 40 per cent. It is well known that the thyroid gland is not necessary for vegetative or invertebrate life, and these researches suggest that the gland is not absolutely necessary for the biologic utilization of iodine, its hormone merely increasing the availability of iodine for utilization by the tissues. Further researches on the latter phases of iodine metabolism should prove of the greatest importance.

The true cause of the increase in the fecal excretion of iodine in exophthalmic goiter is not known. It may be due to an increased concentration of iodine as the inorganic iodide of calcium or as an addition product of calcium iodide. Greenbaum and Raiziss [39] showed that the elimination of iodine after the administration of calcium iodide orally and of an addition product of calcium iodide and thio-urea orally or

37. Curtis, Barron and Phillips.[111] Curtis, Barron and Matthews.[31]

38. Abelin, I.: Ueber die extrathyreoidale Entstehung thyroxinartig wirkender Jodverbindungen, Klin. Wchnschr. **13**:940, 1934.

39. Greenbaum, E. R., and Raiziss, G. W.: The Elimination of Iodine After Oral or Intravenous Administration of Various Iodine Compounds in Single Massive Doses, J. Pharmacol. & Exper. Therap. **30**:407, 1927.

intravenously is entirely different from that subsequent to the administration of sodium or potassium iodide or some organic iodine compounds. Approximately one-half appears in the urine and the remainder in the feces. The iodides of potassium and sodium were eliminated almost quantitatively in the urine. Calcium iodide and its addition products were eliminated more slowly than these other compounds. Furthermore, in partial support of this hypothesis is the occurrence of an increased content of inorganic iodine in the blood in exophthalmic goiter [40] and an increase in the fecal excretion of calcium.

These results emphasize also that the body may excrete an element of which it is in apparent need. This is not applicable to chlorine or to the more permanent storage of iodine which is husbanded by the body. During starvation the excretion of chlorine and of iodine which is mobilized with difficulty [12b] sinks almost to zero. The true significance of this increased negative iodine balance in exophthalmic goiter in the presence of an intake of iodine sufficient for normal subjects and in the presence of an apparent need for iodine remains unknown. This chemical manifestation of the disease becomes still more significant when it is realized that the diffuse hyperplastic thyroid gland retains its natural avidity for iodine, such as in compound solution of iodine or even in diiodotyrosine.

The true fate of thyroid hormone in the organism is, as yet, unknown. But, suffice it to say that in exophthalmic goiter not only the hormonal fraction of the blood but also the other organic fractions and the inorganic fraction of iodine are increased.[40] Elmer and Luczynski [41] have shown also that after gastric administration or intravenous injection of thyroxine into animals, from 90 to 93 per cent of the iodine excreted in the bile and from 49 to 63 per cent of the iodine excreted in the urine are excreted as split products of thyroxine. In addition, Asimoff and Estrin [42] recently found that after feeding dried thyroid gland to dogs and after the intravenous injection of thyroxine the amount of iodine excreted in the urine was increased. This urine in no

40. Elmer, A. W.; Rychlik, W., and Scheps, M.: L'hyperthyroxinémie dans la thyréotoxicose, Compt. rend. Soc. de biol. **117**:533, 1934.

41. Elmer, A. W., and Luczynski, Z.: Sur l'élimination par la bile de la thyroxine administrée par voie entérale, Compt. rend. Soc. de biol. **115**:647, 1933; Sur la décomposition par le foie de la thyroxine injectée dans les veines, ibid. **114**:351, 1933.

42. Asimoff, G., and Estrin, E.: Ueber das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere; der Charakter des Ausscheidung des Schilddrüsenhormons nach peroraler Einführung getrockneter Schilddrüse beim Hunde, Ztschr. f. d. ges. exper. Med. **76**:380, 1931; Ueber das Schicksal des Schilddrüsenhormons im Organismus hyperthyreoidisierter Tiere; der Charakter der Ausscheidung des Schilddrüsenhormons nach Einführung von Thyroxin per os, ibid. **76**:399, 1931.

instance affected metamorphosis of the axolotl. They concluded that the iodine is excreted in the urine in simple compound form.

Elmer [43] has already shown, by giving a moderate dose of diiodotyrosine to men, that one half of the amount given is excreted in the urine in inorganic form. It is possible that some of this iodine is utilized thyroid hormone iodine in such chemical combination that it is not available to the thyroid gland for the formation of its hormone or to the tissues for their utilization. Further investigation of these particular problems concerning the ultimate fate of the thyroid hormone is needed.

In the patient with hypothyroidisim a decrease in the amount of calcium excreted accompanied the decrease in the amount of circulating iodine. In the two patients with exophthalmic goiter an increase in the amount of calcium excreted was associated with the increase in the amount of circulating iodine.

In the patient with exophthalmic goiter who was maintained on a low calcium intake, a study of three periods of three days each revealed the iodine balance to be continuously negative and the calcium balance to vary directly with the iodine balance. In the patient with exophthalmic goiter maintained on a high intake of calcium, a study of five periods of three days each showed that the iodine balance remained at a level definitely lower than that in the two normal controls. The calcium balance varied inversely with the iodine balance. In the other subjects maintained on a low calcium diet, a study of nine of twelve periods of three days each showed that the calcium balance varied directly with the iodine balance.

An interpretation from these data of the correlation of the total calcium and iodine metabolism with the function of the thyroid gland should be made with caution, since only these five subjects, to our knowledge, have been so investigated thus far.

SUMMARY

An investigation of the calcium and iodine metabolism of one totally thyroidectomized patient, two normal subjects and two patients with exophthalmic goiter is reported.

An accurate, more simple and rapid method of determining the calcium content of the urine is presented.

The calcium and phosphorus content of the serum of one totally thyroidectomized subject and two patients with exophthalmic goiter was not appreciably changed.

In the patient with hypothyroidism there was an increased retention of calcium over normal. In the two normal subjects on a low calcium

43. Elmer, A. W.: Di-Iodotyrosine and Thyroid Function, Quart. J. Exper. Physiol. **24**:95, 1934.

diet the calcium balance was negative. In the two patients with exophthalmic goiter there was an increase in the amount of calcium excreted. In one the increase was almost entirely in the feces. In the other the increase was in both the urine and the feces. This resulted in a continuous negative calcium balance greater than normal.

The thyroid gland is the chief organ which maintains the blood iodine at an average normal level.

A study of the blood or of the urinary calcium or iodine alone does not reveal a complete picture of the calcium or iodine metabolism.

The extrathyroid tissues, as well as the thyroid gland, contain a readily available storage of iodine. The more permanent storage of iodine is extrathyroid.

In the two patients with exophthalmic goiter the iodine balance was less than normal even in the presence of an intake of iodine which was at least normally adequate. The increased fecal excretion of iodine was greater than the increased urinary excretion of iodine, thus showing a difference from the findings for normal persons and for subjects with hypothyroidism.

In the patient with hypothyroidism a decrease in the excretion of calcium accompanied the decrease in the circulating iodine. In the two patients with exophthalmic goiter an increase in the excretion of calcium accompanied the increase in the circulating iodine.

In the patient with exophthalmic goiter maintained on a low intake of calcium, observations during three periods of three days each revealed that the iodine balance was continuously negative and that the calcium balance varied directly with the iodine balance.

In the patient with exophthalmic goiter maintained on a high intake of calcium, observations during five periods of three days each showed that the iodine balance remained at a level definitely lower than that of the two normal controls. The calcium balance varied inversely with the iodine balance.

In the other subjects maintained on a low calcium diet, observations during nine of twelve periods of three days each showed the calcium balance to vary directly with the iodine balance.

A SPECIFIC INFECTION CHARACTERIZED BY MULTIPLE ULCERS OF THE SMALL INTESTINE

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The purpose of this paper is to present an unusual and, as far as I know, unique infectious disease, which was characterized especially by a peculiar type of ulceration of the small intestine, from which a specific bacillus was isolated. This organism was capable of reproducing the disease and causing similar lesions in the monkey (Macacus rhesus).

In addition to enteritis there were other specific lesions, such as cholecystitis, cholangeitis, pneumonitis, necrosis of the bone marrow and interstitial nephritis, all of which were reproduced in the monkey after the intravenous injection of the gram-negative bacillus isolated from the patient's bile and intestine.

The clinical features of the case also were anomalous and presented many problems of diagnostic interest, as the following abstract will show.

History.—Mrs. E. B., a 54 year old inhabitant of a small town in the middle of the state of Tennessee, was admitted to the Vanderbilt Hospital on Feb. 13, 1935, in a semicomatose condition. The history obtained was admittedly inadequate owing to the patient's condition. Three months previously she had consulted her local physician because of pain in the region of the liver and slight jaundice. Five weeks before admission to the hospital she was treated for an insect bite on the dorsum of one foot. This responded well to local treatment. About a week later she had a shaking chill and complained of generalized aching. After that she remained ill, with a morning and evening rise in temperature (to from 101 to 103 F.). The urine was said to have contained pus. There was diarrhea, but no description of the stools could be obtained. She had taken little food or fluid for several days before her admission to the hospital.

Physical Examination.—The significant findings were as follows: The temperature was 101.6 F., the pulse rate 104 and the respiratory rate 28. The patient was apathetic and had a yellowish pallor. She was lying perfectly still in bed. She looked ill, and her answers were delayed, short and difficult to understand. Ophthalmoscopic examination revealed a small hemorrhage just inferior to the right disk and a diffusely white area suggestive of old exudate above this disk. The vessels were slightly tortuous. The conjunctivae and mucous mem-

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branes were pale. Fine crackling râles were heard at the base of each lung, and there were several areas of tubular breathing. The apex of the heart was in the left anterior axillary line. There was an occasional extrasystole, but no murmurs were present. The blood pressure was 94 systolic and 46 diastolic. The liver was felt 1 fingerbreadth below the right costal margin. There was tenderness in the right upper quadrant of the abdomen, but no masses were felt. All the normal reflexes were equally active but weak. No Babinski or Kernig reflex was present. On rectal examination large external hemorrhoids were noted, one of them containing a fresh clot. No rectal masses were felt. On removal the examining finger was streaked with brownish blood.

Laboratory Observations.—A catheter specimen of urine showed albumin (2+), an acid reaction, a specific gravity of 1.012, from 5 to 10 white blood cells per high power field, no erythrocytes and only an occasional granular cast.

On February 14 the blood count showed 5,000 leukocytes, 20 per cent polymorphonuclears, 63 per cent lymphocytes, 16 per cent monocytes, 1 per cent myelocytes, 1,430,000 erythrocytes and 5.5 Gm. of hemoglobin. The color index was 1.3. There was no striking variation in the size or shape of the erythrocytes, and their staining properties varied only slightly. A few normoblasts were present. No parasites were noted. The Wassermann and Kahn tests of the blood were negative. On February 14 the nonprotein nitrogen content of the blood was 86 mg. per hundred cubic centimeters, and on February 18 it was 133 mg. The blood sugar content was 121 mg. per hundred cubic centimeters.

The patient's serum failed to show significant agglutinations against Bacillus typhosus, Bacillus paratyphosus A and B, Bacillus melitensis, Bacillus abortus and Bacillus tularensis. On February 14 culture of the blood was sterile.

The cerebrospinal fluid was clear and contained no globulin. There were 4 cells.

Examination of the stool on February 16 showed that it was dark green and formed. It contained bile and occult blood but no parasites.

Roentgenograms showed right dorsal scoliosis. The left ventricle of the heart was slightly enlarged. There was a definite increase in the bronchovascular markings throughout the left lung and the upper lobe of the right lung. Calcified glands were present in the apex of the right lung. No exudation or consolidation was present.

Gastric analysis showed that free hydrochloric acid was absent. The total acid was 57 degrees during fasting. After the administration of alcohol free acid was still absent, and the total acidity was 25 degrees. No histamine was given because of the patient's condition.

Course.—Because of the severe anemia the patient was given two transfusions of 500 cc. of blood (on February 15 and 16) with slight, if any, benefit. The temperature remained high, from 102 to 104 F. On the evening of February 16 Cheyne-Stokes respiration developed, and the patient became comatose. The following day from 400 to 500 cc. of bright red liquid blood was passed by rectum; it did not come from the external hemorrhoids. The respiration became shallow and rapid. The blood pressure was 100 systolic and 40 diastolic. The next morning (February 18) the blood pressure fell to 70 systolic and 20 diastolic, and the pulse rate increased. The patient failed to respond to caffeine and hypodermoclysis and expired from an undetermined cause on the fifth day of hospitalization.

Gross Postmortem Observations.—There were ecchymotic spots on each arm, particularly at the elbow. A few smaller subcutaneous hemorrhages were seen

over other parts of the body. The conjunctivae were pale, and there were two petechiae in the right eye. There was a punched-out ulcer in the mucous membrane of the mouth at the junction of the upper lip and the upper jaw. The upper edge of a plate replacing the upper teeth just reached and was in contact with this ulcer.

Serous Cavities: All the serous cavities were normal, except the pleural cavities, which had a few old adhesions.

Heart: The heart weighed 300 Gm. and showed no abnormality.

Lungs: About half the upper lobe of the right lung was red and congested; it fairly dripped fluid. This area was firmer than the remainder of the lung, and crepitation was diminished, suggesting an early stage of a pneumonic process with edema.

Gastro-Intestinal Tract: The mucosa of the stomach appeared atrophic and had many petechial hemorrhages. No ulcers were present either in the stomach or in the duodenum. Beginning at a point in the jejunum about 3 feet (92 cm.) distal to the duodenojejunal flexure there were occasional places where the mucosal folds were slightly thicker, firmer and more prominent than normal. Some of these areas of thickening measured no more than 4 or 5 mm. in diameter. In several there was a sharp umbilication in the center, at the base of which was hemorrhage. The ulcers became more numerous and larger in the lower portion of the jejunum. At the junction of the jejunum and the ileum there were ulcers at intervals of not more than 12 inches (30 cm.) characterized by round, raised edges and a dirty grayish center. Blood was present in some of the craters. These ulcers appeared to be confined to the mucosa and submucosa. They occupied various positions in relation to the circumference of the intestine; however, most of them were near the mesenteric attachment. The serosa opposite the ulcers had no tubercle formation or other abnormality. In general the ulcers increased in size as the ileocecal valve was approached, where the largest one measured about 3 cm. in diameter. The ulcers showed no definite relation to the lymphoid tissue. Most of Peyer's patches were inconspicuous, and certainly they were not hyperplastic. In one instance an ulcer encroached partly on a Peyer patch without any apparent involvement of the remainder of the patch. The terminal 30 inches (76 cm.) of the ileum had several of these ulcers per foot (30 cm.). There was one firm nodule in the first portion of the ileum, which measured about 5 mm. in diameter; it was raised about 3 mm. above the surrounding mucosa and had an ulcerated but not umbilicated surface. Smears and cultures were made from material taken from this and also from the umbilicated ulcers.

No ulcers were found in the cecum or colon. In the descending colon and sigmoid flexure there were about twenty small diverticula. These measured only a few millimeters in diameter and contained blood that varied from bright red to a dark hue. There was an internal hemorrhoid.

The contents of the duodenum and jejunum were covered with bile. The terminal portion of the ileum and the colon contained dark red, blood-tinged fecal material. The mesenteric nodes were not enlarged, and they appeared normal.

Liver: The liver weighed 1,910 Gm. Minute yellow dots suggested necrosis. The gallbladder was distended with golden brown, cloudy bile. A culture was taken with aseptic technic before the organ was opened. There were no stones, and the mucosa was not remarkable grossly.

Spleen: The spleen weighed 290 Gm. On the cut surface a uniformly red pulp everted the capsule. The organ was fairly firm and somewhat friable. The malpighian bodies were not prominent. The spleen was highly cellular, with the

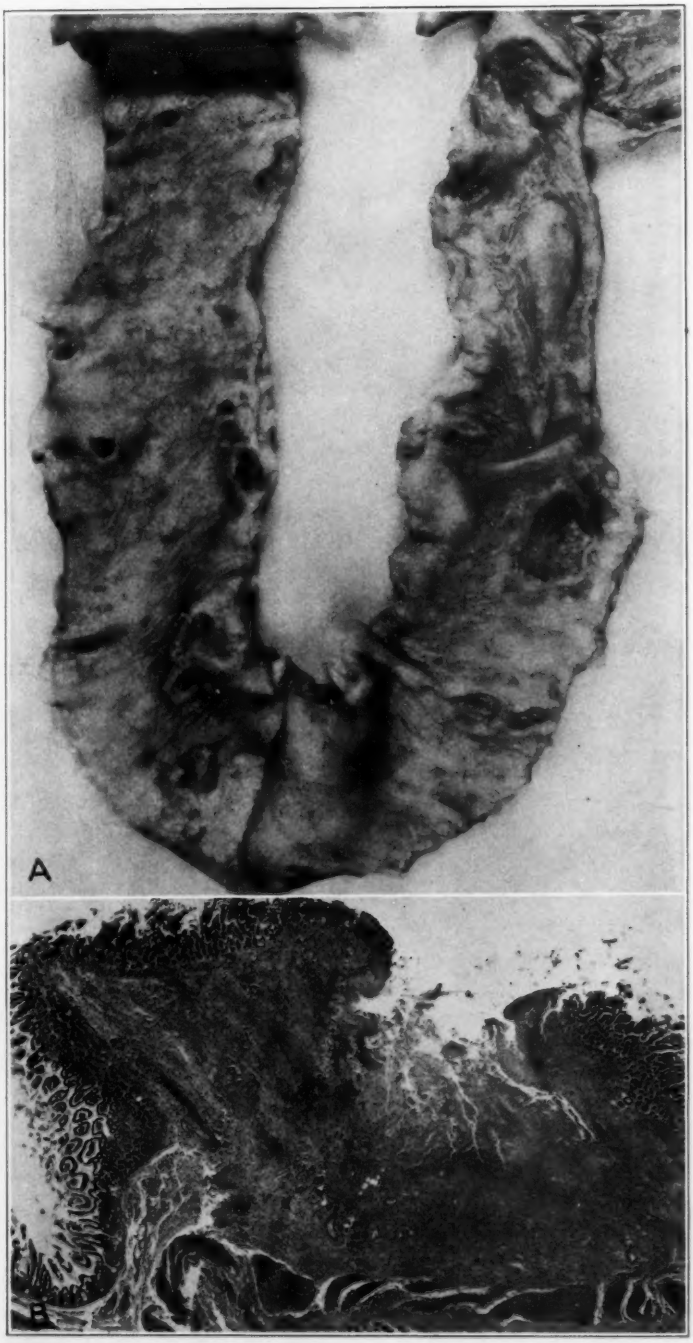

Fig. 1.—*A*, the terminal portion of the ileum, showing ulcers which have no fixed relation to the lymphoid tissue or to the circumference of the intestine. *B*, cross-section of the lower portion of the jejunum, showing ulceration in an inflammatory nodule; × 16.

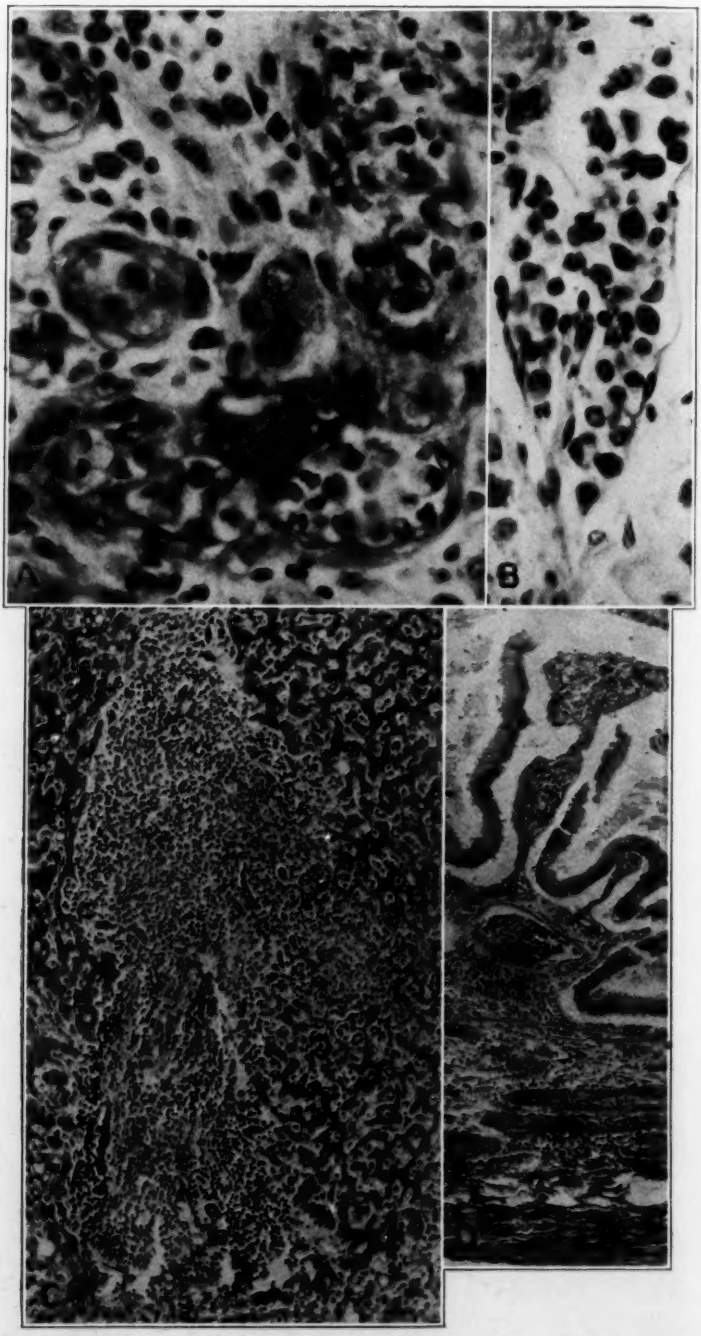

Fig. 2.—*A*, photomicrograph of a vessel in an inflammatory nodule of the intestine, showing inflammation, an early stage of necrosis and beginning thrombosis; × 600. *B*, two lymphatic vessels in an inflammatory nodule of the intestine loaded with large mononuclear cells; × 500. *C*, cross-section of the liver, showing inflammation about the portal area, cholangeitis and periportal necrosis; × 100. *D*, cross-section of the gallbladder, showing inflammation of the wall, particularly about a vessel in the submucosa which is loaded with mononuclear phagocytes and leukocytes. There is a small area of necrosis just below the vessel; × 100.

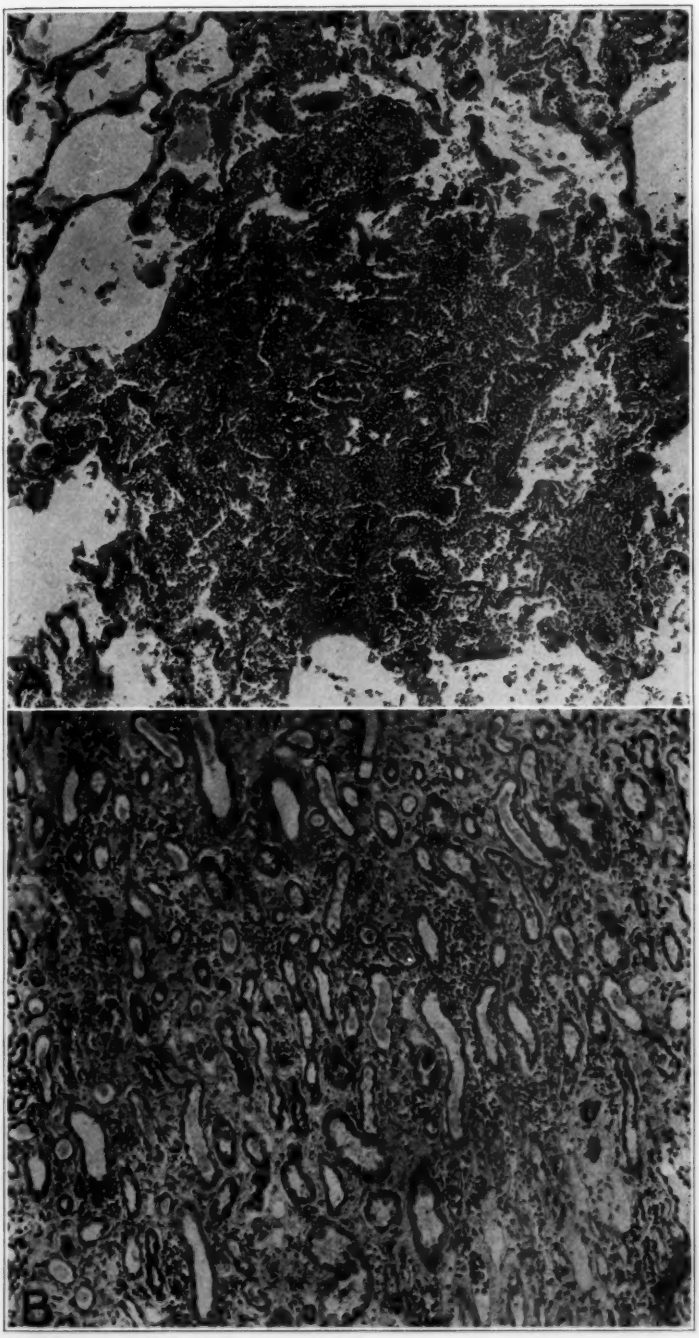

Fig. 3.—*A*, section of the lung, showing an area of inflammation and necrosis with an early stage of abscess formation. Such lesions are not in association with the bronchi but of vascular origin; × 100. *B*, section of the kidney, showing focal accumulations of lymphocytes, mononuclear phagocytes and plasma cells in the interstitial tissue; × 100.

appearance and increased size of an acute splenic tumor of the red type. However, it was firmer than is usually the case in typhoid.

Pancreas and Adrenal Glands: These organs were normal.

Kidneys: The right kidney weighed 240 Gm. and the left 215 Gm. The capsule stripped off with ease, leaving a smooth, pale, swollen surface with a few petechial hemorrhages. The cortical striations were not distinct and regular, but there was no narrowing of the cortex. There were opaque focal areas in the cortex which were thought to represent necrosis. Considerable peripelvic hemorrhage was noted in each kidney, and there were petechial hemorrhages in the mucosa of the pelves and ureters. The right pelvis and ureter were slightly dilated, but no contributing cause could be found.

Bladder: The urinary bladder was normal.

Internal Genitalia: There was hemorrhage in the endometrium and also in the vaginal mucosa.

Bone Marrow: The vertebral marrow was red and appeared to be normal. Owing to restriction of the autopsy no marrow was taken from the femur.

Microscopic Postmortem Examination.—Lungs: Sections of the upper lobe of the right lung showed embolic interstitial pneumonia with hyaline thrombi in the capillaries of the alveolar walls and many leukocytes, with an early stage of necrosis and beginning abscess formation. These lesions were entirely vascular and had no relation to the bronchi. A section of the left lung shows a solitary abscess in an early stage, with surrounding emphysema. There was moderate sclerosis of the arteries and arterioles.

Gastro-Intestinal Tract: The mucosa of the stomach was atrophic. Sections of the jejunum and ileum showed inflammatory nodules in the submucosa. These inflammatory foci were composed of a vascular fibrous stroma, lymphocytes, plasma cells, large mononuclear phagocytes and a few polymorphonuclear leukocytes. The mucosa was intact over many of these nodules, but there was ulceration over others. Regardless of whether the mucosa was ulcerated or not, a striking feature was the inflammation of the blood vessels, both arterioles and veins, in these nodules. Some of the vessels showed an early stage of thrombosis and polymorphonuclear leukocytes in the wall, and a few could be definitely associated with small pustules. Few polymorphonuclear leukocytes were seen except in connection with these vascular lesions or on the surface of the ulcers. Many lymphatic vessels contained large mononuclear phagocytic cells. In a few instances the lymphocytes, plasma cells and large mononuclear cells were invading the muscularis and even extended into the subserosa.

Liver: There were cholangeitis characterized by infiltration of round cells, a few large mononuclear phagocytes and only an occasional polymorphonuclear leukocyte about the portal triads. Many focal areas of necrosis were present, particularly in the region of the central vein. These foci of necrosis contained many large mononuclear cells but only a few polymorphonuclear leukocytes.

Gallbladder: The submucosa and the muscularis were distended by edema and infiltration of round cells, large mononuclear cells and polymorphonuclear leukocytes. There were foci of necrosis which had a definite relation to blood vessels. Several small vessels showed an early stage of thrombosis and some inflammation. The mucosa was intact. There was much fibrosis in the subserosa, with slight round cell infiltration.

Spleen: Many sinusoids and a few vessels contained hyaline thrombi. There was congestion of the sinusoids with red blood cells and conspicuously large numbers of plasma cells, which were abundant also in the pulp. There was hyaliniza-

tion in several of the malpighian bodies. A few eosinophilic and neutrophilic myelocytes were present. There were also a few megakaryocytes and normoblasts. Several miliary abscesses were present in the pulp. These showed leukocytic infiltration and fragmentation of the nuclei and were surrounded by a zone of hemorrhage. Many phagocytic cells contained hemosiderin pigment. There was slight arteriolar sclerosis.

Kidney: There was extensive parenchymatous degeneration of the convoluted tubules, with desquamation of the epithelium and in some instances epithelial regeneration. Many foci of lymphocytes, plasma cells and large mononuclear cells were present in the interstitial tissue of the cortex and medulla. There was hemorrhage about the pelves. A few lymphocytes, plasma cells and polymorphonuclear leukocytes and rare myelocytes were present in the peripelvic tissue. The glomeruli were normal.

Bladder: There was hemorrhage into the mucosa.

Bone Marrow: The vertebral bone marrow was hyperplastic, but few adult polymorphonuclear cells were present. A few myelocytes and myeloblasts were seen, and there were many megakaryocytes and normoblasts. The predominating cells were the large mononuclear phagocytes. There were scattered plasma cells and lymphocytes, with some foci of the latter. In addition to this chronic inflammatory process, there were many small focal areas of acute necrosis, with a concentration in them of polymorphonuclear cells and mononuclear phagocytes.

The essential features in this case were the anemia, the intestinal ulcers, the focal necrosis in the spleen, bone marrow and liver, the cholecystitis, the cholangeitis, the pneumonitis and the interstitial nephritis.

A gram-negative capsule-forming bacillus was recovered from the bile and the intestinal ulcers which seemed to belong to the Bacillus mucosus-capsulatus group. This organism was capable of reproducing similar lesions in the monkey (M. rhesus). The source and portal of entry of the organism into the body were obscure.

BACTERIOLOGY

Cultures of material from the ulcers in the small intestine and from the bile revealed a gram-negative bacillus which was small but which varied slightly in length. It grew abundantly on ordinary mediums. On plain agar the colonies were entire, glistening, convex and mucoid. In infusion broth the abundant growth gave a turbid appearance, a ring was formed at the top and there was sediment. Gas formed in ordinary infusion broth. The micro-organism grew anaerobically with the production of gas. It was nonmotile. Capsules were formed after incubation for from twenty-four to forty-eight hours in infusion broth. The organism was nonhemolytic.

The organism fermented mannitol, xylose, dextrose, maltose, levulose, inositol, lactose, sucrose and rhamnose, all with the production of gas. It did not ferment dulcitol. There was no formation of indole in peptone water.

Serology.—Fortunately a sufficient amount of the patient's serum was saved for the following agglutinations:

Patient's serum against		Titer
	Unknown organism from ulcer in patient's ileum	1:2,560
	Unknown organism from ulcer in patient's ileum after several transfers in infusion broth	1:20,480
	Unknown organism from patient's bile	1:20,480
	Stock strain of B. typhosus	No agglutination
	Stock strain of B. paratyphosus A	1:20
	Stock strain of B. paratyphosus B	No agglutination
	Stock strain of Bacillus lactis-aerogenes	1:80

From this tabulation it is apparent that serologically unknown organisms obtained from the bile and from the ulcers in the small intestine of the patient were identical. Furthermore, there seemed to be no serologic relationship between this unidentified bacillus and members of the typhoid group or B. lactis-aerogenes.

In order to determine whether the serums of average persons possess any agglutinins against this organism, the serums of six normal subjects were pooled and used in agglutination experiments:

	Titer
Pooled normal serum (human) against unknown organism from ulcer in patient's ileum	1:10

The foregoing data present conclusive serologic evidence not only that the patient harbored the unknown organism but that this organism was active in producing agglutinins, which the average person has only in a small titer or not at all.

It was impossible to do further serologic tests with the patient's own serum because of the limited amount available. In order to obtain serum for further identification work, rabbits were immunized by subcutaneous inoculations with the unidentified bacillus.

Eleven subcutaneous inoculations of 0.5 cc. of fresh twenty-four hour infusion broth culture of the unknown organism were given to each rabbit at three day intervals. In several cases an abscess developed at the site of the inoculation. Ten days after the completion of these inoculations blood was drawn, and the serum was separated for further work on identification. In the following tabulation the immunized rabbit serum was used against known stock strains of the listed organisms which seemed most closely related to the unknown organism both morphologically and according to cultural characteristics:

Serum of rabbit immunized against unknown organism against		Titer
	Unknown organism	1:2,560
	Organism from ulcer in colon of monkey 2	1:2,560
	Bacillus lactis-aerogenes	1:80
	Escherichia coli	1:20
	Bacillus proteus X19	1:40
	Bacillus cloacae	1:10
	Bacillus Friedländeri	No agglutination
	Bacillus Friedländeri E. G. S.	No agglutination
	Bacillus Friedländeri K.	No agglutination

From this tabulation it is apparent that immunized rabbit serum gave a high titer against the infecting organism but failed to show high titers against the known organisms with which it might possibly be confused by morphologic or cultural characteristics.

This organism appeared to be rather closely related to B. lactis-aerogenes. However, rabbits immunized against a stock strain of B. lactis-aerogenes failed to confirm this relationship:

		Titer
Serum of rabbit immunized with B. lactis-aerogenes against	B. lactis-aerogenes	1:2,560
	Organism isolated from ulcer in patient's ileum	No agglutination
	Organism from patient's bile	No agglutination
	Organism from ulcer in colon of monkey 2	No agglutination

Thus the serum of rabbits immunized against B. lactis-aerogenes agglutinated this organism to the titer of 1:2,560 but failed to agglutinate the unknown bacillus. This is convincing evidence against its being B. lactis-aerogenes.

As will be described under animal experimentation, four monkeys were inoculated intravenously with the unknown micro-organism. Two of these (monkeys 1 and 2) came to autopsy, and the bacillus was recovered in each instance from lesions in the intestine. The two other animals (monkeys 3 and 4) lived and their serums showed agglutinations as follows:

		Titer
Serum of monkey 3 infected (66 days) with organism from ulcer in patient's ileum against	Same organism	1:20,480
	B. lactis-aerogenes	1:640
	B. Friedländeri K.	1:5,120
Serum of monkey 4 infected (40 days) with organism from ulcer in patient's ileum against	Same organism	1:2,560
	B. lactis-aerogenes	1:40
	B. Friedländeri K.	1:320

Thus in the monkeys a very high titer developed against the infecting organism, and relatively high titers developed against B. lactis-aerogenes and B. Friedländeri K. These two organisms seemed most closely related to the unknown micro-organism isolated from the patient's bile and the ulcers in the patient's ileum. As a control for these agglutinations, serum of normal monkeys was tested, and it failed to agglutinate the unknown micro-organism or the stock strain of B. lactis-aerogenes.

ANIMAL EXPERIMENTATION

Mice.—As little as 0.02 cc. of a twenty-four hour infusion broth culture of the unknown micro-organism killed mice when it was injected intraperitoneally. The mice died of peritonitis and septicemia in from one to three days.

Rabbits.—Subcutaneous inoculation of the unknown micro-organism produced only a local inflammatory reaction and the development of immunity.

Monkeys.—Monkey 1.—On February 27 3 cc. of a twenty-four hour infusion broth culture of the unknown bacillus (isolated from material from the ulcers in the intestine and from the bile of the patient) was given to this monkey intravenously. The animal passed fresh blood in loose stools on the fourth and fifth days. The diarrhea continued, and the animal died on March 7, the ninth day after the inoculation. Blood counts and determinations of hemoglobin on the fifth day failed to show any significant anemia or other changes in the blood.

The gross lesions of significance were confined to the colon, particularly the cecum and the ascending colon, where there was an acute diffuse inflammatory process, with marked edema and necrosis of the mucosa. No localized ulcers were present. The unknown organism was recovered from the colon.

The significant findings were diffuse colitis with necrosis of the mucosa and thrombosis of some of the vessels in the submucosa. In addition there were minimal cholangeitis and marked parenchymatous degeneration of the kidneys, with some hydropic degeneration of the tubular epithelium.

Monkey 2.—In an attempt to produce enteritis in this animal after the oral administration of the bacillus, a stomach tube was passed on March 12, and

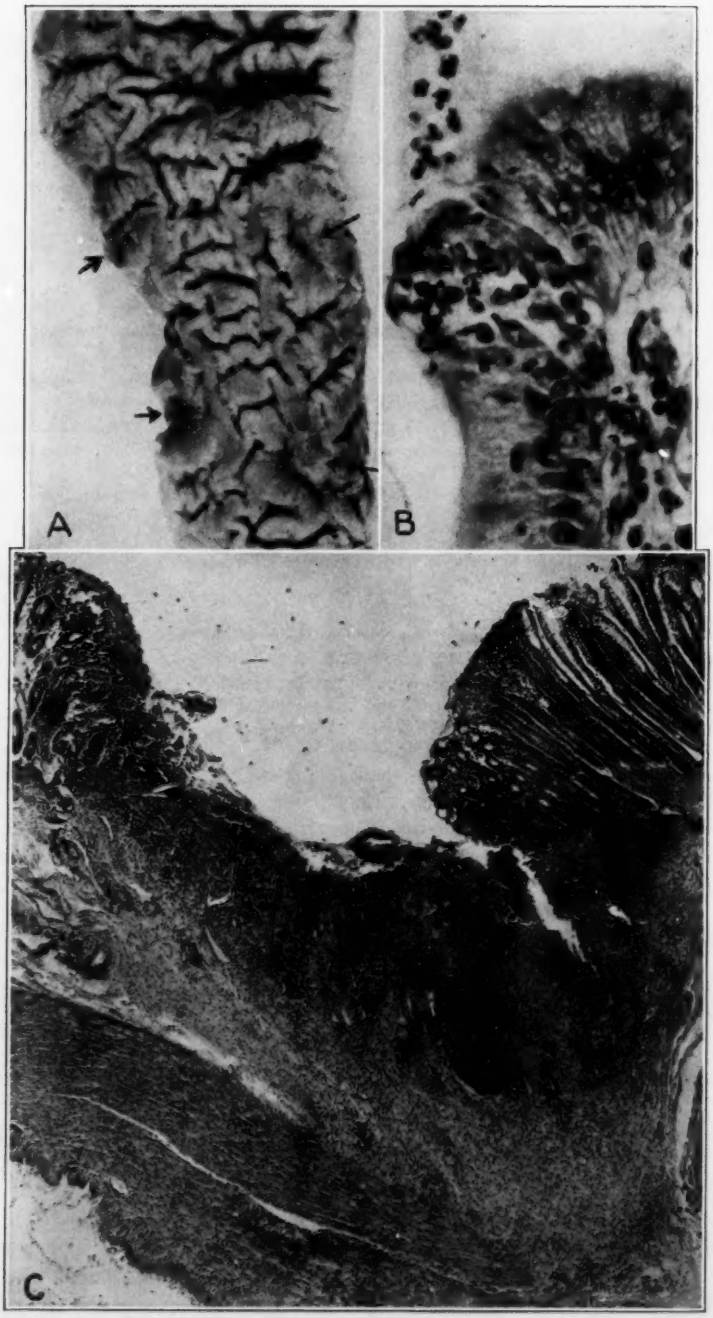

Fig. 4.—*A*, the ascending colon of monkey 2, showing several well defined ulcers (indicated by arrows). *B*, section of the galdbladder of monkey 2, showing acute inflammation of the mucosa and submucosa; × 475. *C*, section of an ulcer in the ascending colon of monkey 2, showing an absence of the mucosa and acute and subacute inflammation of the submucosa, with a slight increase in the fibrous tissue near the muscularis; × 44.

4 cc. of fresh twenty-four hour infusion broth culture of the original unknown organism was injected into the stomach. There was no diarrhea or suggestive evidence of infection during the succeeding eleven days. On March 23 the animal was given 4 cc. of the infusion broth culture of the unknown organism intravenously. Diarrhea developed four days later, but there was no blood in the stools. This diarrhea continued; the animal became sick but soon began to improve. On April 4 (the twenty-third day after the intravenous inoculation) it was killed.

There were several small abscesses in the lungs and one in the liver. The entire gastro-intestinal tract was edematous, and there were several small, well defined ulcers in the colon, similar to those noted in the patient's ileum.

The liver showed cholangeitis characterized by infiltration by round cells and polymorphonuclear leukocytes about the portal triads. A section taken through the abscess showed in the gross an attempt at encapsulation with a wall of lymphocytes, polymorphonuclear leukocytes and some fibrous tissue. The gallbladder showed edema of the entire wall, with marked cellular infiltration. Many round cells and polymorphonuclear leukocytes were between the muscular layers and in the mucosa. In one area polymorphonuclear leukocytes were passing through the mucosa into the lumen of the gallbladder. The gastro-intestinal tract showed edema throughout. No ulcers were present in the small intestine, but in the colon, in addition to slight infiltration of the mucosa with polymorphonuclear leukocytes, there were well defined ulcers in the mucosa, with marked inflammation even down into the submucosa. On the surface of the ulcers were blue, amorphous clumps of bacteria, and beneath these there was much acute and subacute inflammation, with some increase in the amount of fibrous tissue, particularly deep near the muscularis. The kidney showed focal accumulations of lymphocytes and large mononuclear cells in the interstitial tissue, giving the typical appearance of interstitial nephritis. The tubules showed marked parenchymatous degeneration. The bone marrow showed focal accumulations of leukocytes and petechial hemorrhages, but no significant changes were observed in the myeloblastic or erythroblastic tissues. The spleen was loaded with leukocytes, and the malpighian bodies showed marked hyperplasia with some necrosis. Many phagocytic cells contained hemosiderin pigment.

The blood culture was sterile. The original bacillus was recovered in pure culture from the bile and predominated in cultures of material from the ulcers in the colon of this monkey.

Monkey 3.—On March 12 this monkey was given intravenously 3 cc. of a twenty-four hour infusion broth culture of the original organism. The animal appeared to be acutely ill for several days, but it recovered without evidence of enteritis. On May 18 blood was drawn for agglutination purposes (see the tabulation in the previous section, on bacteriology).

Monkey 4.—In order to determine the amount of anemia produced in this animal, blood counts were made before inoculation with the organism and after an interval of five weeks. On April 8 the blood count showed 6,190,000 erythrocytes, with 14 Gm. of hemoglobin. On the same day 3.5 cc. of twenty-four hour infusion broth culture of the organism recovered from the bile of monkey 2 (which was identical with the original organism obtained from the patient) was given intravenously to this monkey. Six days later there was diarrhea without blood, which continued for about five days. On May 13 a blood count showed 4,050,000 erythrocytes, with only 10 Gm. of hemoglobin, thus indicating definite

anemia. On May 18 blood was drawn for serologic work (see the tabulation in the previous section on bacteriology).

Two attempts to produce the infection in monkeys by subcutaneous injection were unsuccessful, as only localized induration followed.

COMMENT

The two common types of specific ulceration of the small intestine are (1) that due to B. typhosus, characterized by ulceration of Peyer's patches and the solitary follicles and (2) that due to the tubercle bacillus, which, as in typhoid in its earlier stages, is confined to the lymphoid tissue of the small intestine and colon. In addition to these, not infrequently the dysentery group of organisms cause lesions in the terminal ileum as well as in the colon.

Nonspecific solitary and multiple ulcers have been described in the small intestine. Many of these have been called peptic ulcers of the small intestine. No etiologic micro-organism has been isolated and proved to be the cause of any of this group of conditions.

The ulceration in the case reported here differs from the usual types in the small intestine in two principal ways: (1) etiologically, since an unclassified gram-negative capsule-forming bacillus was isolated from the ulcers and from the bile of the patient, and all evidence points to it as the cause of the ulceration; (2) anatomically, since the distribution of the ulcers without definite relation to the lymphoid tissue or to the circumference of the intestine differs from that seen in the ordinary types of enteritis.

The ulcers in this case were present in the upper portion of the jejunum, and they increased in number near the ileocecal valve. They showed no definite or constant relationship to the lymphoid tissue or the circumference of the intestine. Peyer's patches and the solitary follicles were not hyperplastic. The ulcers were seen more frequently on the mesenteric than on the antimesenteric side of the lumen. The earliest lesions began as inflammatory nodules in the submucosa, with what appeared to be primary involvement of the vessels in this area. Later the mucosa over the nodules became necrotic, and ulceration of the mucosa and submucosa resulted.

While the enteritis was of primary importance because of its unusual etiologic and anatomic features, the cholecystitis, cholangeitis, interstitial nephritis, inflammation of the bone marrow and pneumonia also were of great importance, because they were apparently caused by the same bacillus and undoubtedly contributed greatly to the patient's death.

The specific gram-negative bacillus was agglutinated by the patient's own serum in a titer of 1:20,480. Infusion broth cultures when injected intravenously into the monkey reproduced ulcers in the colon similar to those noted in the small intestine of the patient. The bacillus

was again isolated from the ulcers in the monkey's colon in almost pure culture and from the bile in pure culture.

Cholecystitis, cholangeitis, pneumonitis and interstitial nephritis similar to those in the patient were reproduced in the monkey after intravenous inoculation of the unclassified micro-organism.

The specific bacillus undoubtedly belongs to the general group of encapsulated gram-negative bacilli with which B. lactis-aerogenes, Bacillus pneumoniae of Friedländer, Bacillus acidi-lactiti and Bacterium rhinoscleromatis are associated. Identification of this bacillus is difficult because it does not conform to any of the known strains in all its characteristics. Like Bacillus lactis-aerogenes it ferments dextrose, saccharose and lactose, and in this respect may be said to differ from the others, none of which is said to ferment all of these sugars. However, even this is a questionable differentiation, as fermentations are often so variable. Serologically it differs from B. lactis-aerogenes and Friedländer's bacillus (see the tabulation in the previous section, on bacteriology). The patient's and the rabbit's serum gave definite evidence of individuality; however, monkey serum was not so conclusive. Thus, morphologically, culturally and serologically this bacillus appears to be a distinctive strain but has not been positively identified, because of the marked variations in the members of this group. However, its pathogenicity certainly places it in a class by itself.

There is some resemblance between this infection and typhoid. Both are marked by leukopenia, an exudate of mononuclear cells in the intestinal ulcers, focal necrosis in the spleen, the bone marrow and the liver and cholecystitis with infection of the bile. However, the type and distribution of the intestinal ulcers and the etiologic organisms in these two diseases are entirely different.

The marked parenchymatous degeneration and especially the interstitial nephritis are evidences of intoxication. The interstitial nephritis is similar to but more severe than that in such infectious diseases as scarlet fever and diphtheria.

The question of antecedent pernicious anemia is pertinent. The color index of 1.3 and absence of free hydrochloric acid in the stomach strongly suggest such a possibility, but the absence of a striking variation in the size, shape and staining characteristics of the red blood cells is against this assumption. The anemia might have been due to loss of blood in the intestine, intoxication and necrosis of bone marrow resulting from the specific infection.

In the absence of any illuminating evidence in the history which might suggest the source and mode of infection, no conclusive pathologic observations throw light on these important points. However, the vascular lesions in the intestine, gallbladder and lung, along with

the interstitial nephritis and the inflammation of the bone marrow and spleen, suggest that the organism was blood borne. Although cultures of the blood made four days before death and at the time of autopsy were sterile, it is entirely possible that the unknown organism had been present in the blood earlier in the disease.

The patient's history of an insect bite on the foot a week before she became ill suggested the possibility that the bacillus gained entrance through the skin. In following this lead, subcutaneous inoculation of the organism in monkeys and rabbits failed to show more than a localized response and the development of immune bodies. Monkeys given the bacillus by mouth (stomach tube) failed to show any evidence of enteritis or infection.

SUMMARY

A report is made of a peculiar case of ulceration of the small intestine in which there were cholangeitis, cholecystitis, interstitial nephritis, pneumonitis and inflammation and necrosis of the bone marrow.

A gram-negative capsule-forming bacillus was isolated from the intestine and from the bile which was capable of reproducing similar lesions in the monkey (M. rhesus).

This unclassified specific bacillus is possibly related to the B. mucosus-capsulatus and B. lactis-aerogenes groups, although it is immunologically distinct.

CLINICAL ASPECTS OF PERIARTERITIS NODOSA

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In the sixty-five years since periarteritis nodosa was presented as a disease entity by Kussmaul and Maier, the accrued pathologic and clinical material has helped to clarify the conception of its symptomatology and pathogenesis. First considered solely as a medical curiosity, periarteritis nodosa now is known to be of significance in relation to certain other syndromes which, though more familiar, are none the less still obscure.

In the classic case of Kussmaul and Maier [1] the condition was at first considered clinically to be trichiniasis. These observers, therefore, regarded the diagnosis of periarteritis nodosa as possible if symptoms suggesting trichiniasis occurred in association with nephritis and enteritis and if biopsy of a muscle nodule showed pericapillary cellular infiltration but no trichinas. Since then, however, every discussion has emphasized the protean manifestations and the rarity of a correct diagnosis during life. P. S. Meyer (1878) suggested as the diagnostic formula of periarteritis nodosa the triad of "chlorotic marasmus," polymyositis and polyneuritis, and gastro-intestinal symptoms.

Successive observers recognized the wider clinical range of this malady. Thus Harbitz [2] in 1927 distinguished six types—gastro-intestinal, renal, neuromuscular, cardiac, cerebral and cutaneous. Singer [3] made the following more comprehensive statement:

> The bewildering symptomatology of the disease can be rendered least intricate by assuming the presence of an infectious process which, in addition to producing general disturbances such as fever, tachycardia, prostration, cutaneous eruptions and leukocytosis, causes symptoms based on circulatory disturbances in the systems or regions affected.

From Singer's summary it is apparent that almost innumerable combinations of symptoms involving different systems are possible and even predictable; indeed, new ones are reported frequently.

From the Mount Sinai Hospital.

1. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med **1**:484, 1866.

2. Harbitz, F.: Different Forms of Arteritis, Especially "Periarteritis Nodosa," Internat. Clin. **3**:130, 1927.

3. Singer, H.: Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations: Report of Two Cases, Arch. Int. Med. **39**:865 (June) 1927.

This sketch of the syndrome is not complete without emphasis on one real though intangible clinical characteristic—the disproportion between the number and intensity of the symptoms and the disease which is assumed to be their cause; thus the diagnosis that is made generally seems a little strained and not quite apt. Because of the variability in the occurrence of symptoms, periarteritis nodosa has mimicked other conditions and, even with the aid of biopsies, has been diagnosed correctly in only about 12 per cent of the reported proved cases. However, in very recent years diagnoses have been much more accurate.

SUMMARY OF THE PATHOLOGIC OBSERVATIONS

The pathologic condition to which the syndrome owes its name is the picturesque appearance of gross aneurysmal dilatations of the arteries. This, however, has been mentioned in only a minority of the cases and is not the essential characteristic. The pathologic pattern is a primary injury to the wall of the vessel with swelling, necrosis and fibrillation of the media, destruction of the elastica interna and infiltration of the adventitia with polymorphonuclear leukocytes, which are often eosinophilic, and also with many histiocytes.

A variety of vascular lesions may occur secondary to this initial lesion, for instance, aneurysms at the site of weakening of the vessel wall, hemorrhages or thromboses, with a train of symptoms based on these mechanical complications. Tendencies to healing occur, as manifested by fibrosis of the involved vessels or recanalization of thrombosed vessels. However, this histologic healing frequently results in clinical disease, since there is injury to tissues and organs due to local nutritional changes. Manges and Baehr [4] studied a case in which successive biopsies were made of affected vessels at three stages during the clinical course. They demonstrated that the degenerative lesions of the vessel walls seen in some of the previously reported cases were the late "healed" sequelae of an earlier acute inflammatory process.

These vascular changes are most extensive on the arterial side of the circulation and, more specifically, of the medium-sized arteries, including the vasa vasorum of large arteries. Veins also are involved but to a remarkably less extent in respect to the rapidity of development of the process, the severity of the lesion and the number of involved vessels. Capillary injury, such as occurred in the muscle in the case reported by Kussmaul and Maier, produces various symptoms and may be manifested by purpura and urticaria. The vascular lesions are most frequently generalized, though some instances have been reported in

4. Manges, M., and Baehr, G.: Periarteritis Nodosa, Am. J. M. Sc. **162**: 162 (Aug.) 1921.

which they were limited to one or a few organs (Fishberg [5]). One may surmise that many such lesions occur but escape clinical notice. Besides these vascular lesions, granulomatous nodules of the serosal membranes have been noted occasionally.

The tempo of the course may be acute, subacute or chronic. Manges and Baehr called attention to the fact that both acute and healing lesions may be present in the same case. Though the name denotes vascular involvement, parenchymatous degeneration of tissue occurs which is not directly dependent on local arterial lesions.

Periarteritis nodosa is not restricted to the human species.[6] An epidemic infectious disease among deer and also among swine has been noted in which similar lesions were present. This fact suggested that these species might be the reservoir of an unknown virus, a relation similar to that of lower animals and the virus of typhus fever.

Opinions as to etiologic factors have reflected changing medical concepts, and only recently has any suggestive experimental evidence been adduced. Because the periarteritic nodules were proved to be aneurysms, the cause, particularly in pre-Wassermann-test days, was attributed to syphilis. The patient reported on by Chvostek and Weichselbaum [7] (1877) had encephalitic symptoms, including disturbed pupillary reflexes. On the basis of these clinical findings and the resemblance between the periarteritic lesions and the perivascular lesions of syphilis, a common cause for the two conditions was assumed. In the case reported by Schmorl [8] (1903) the diagnosis of periarteritis nodosa was established by biopsy in a woman aged 53, and antisyphilitic therapy was instituted. When the patient died, two years later, of acute thrombosis of the portal vein, widely distributed healed lesions of periarteritis nodosa were observed. Syphilis was assumed to be the cause, owing to the so-called therapeutic test. This observation is not of etiologic significance, since lesions of periarteritis nodosa may heal spontaneously. Of 30 recent cases of periarteritis nodosa, Gruber [9] cited a history of syphilis in 3 and a positive Wassermann reaction in 2. Spirochetes have never been demonstrated in the tissues in a case of undisputed periarteritis nodosa. On evidence of this kind it appears that the relationship between syphilis and periarteritis nodosa is certainly not unusually close.

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5. Fishberg, A.: Zur Kenntnis der Periarteritis nodosa insbesondere der Histiopathogenese, Virchows Arch. f. path. Anat. **240**:483, 1923.

6. Joest, E., and Harzer, J.: Ueber Periarteriitis nodosa beim Schwein, Beitr. z. path. Anat. u. z. allg. Path. **69**:85, 1921.

7. Chvostek and Weichselbaum: Herdweise syphilitische Endarteritis mit Aneurysmenbildung, Allg. Wien. med. Ztg. **22**:257, 275 and 294, 1877.

8. Schmorl, cited by Gruber;[9] Verhandl. d. deutsch. path. Gesellsch. **6**:203, 1903.

9. Gruber, G. B.: Zur Frage der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **258**:441, 1925.

Eppinger[10] suggested an intrinsic weakness of the vascular system as the essential predisposing factor (1887). Dietrich[11] suggested that a reflex nervous involvement of the vascular wall is the underlying mechanism (1933).

The syndrome has been considered also a specific infectious disease. Attempts to reproduce the disease in lower animals by inoculation of crushed nodules and subinoculation have been inconclusive (Harris and Friedreich[12]). Klotz[13] in 1917 claimed to have initiated the essential lesions of the disease in rabbits by means of injections of streptococci, but aneurysms and thromboses were absent. Metz in 1931 produced lesions of a periarteritic type but without aneurysms in rats. The animals were first highly sensitized to streptococci, and then either these organisms or nonspecific serum was injected. This experimental work is in accord with Gruber's conception of periarteritis nodosa as a peculiar hyperergic expression of the sensitized portions of the arterial walls of one or several organs in the course of some prolonged infection or septic disease.

The standard clinical features have been well described by a number of writers. A miscellany of additional variations in symptomatology will be presented here from a series of cases of proved periarteritis nodosa studied at the Mount Sinai Hospital in the last fifteen years,[14] and also 2 from the St. Vincent's Hospital, of Staten Island, New York.[15] The case histories are given in detail, but the summary which follows each report is sufficient for reference purposes.

REPORT OF CASES

Case 1.—A. M., a Mexican aged 33, gave a history of gonorrhea, repeated sore throats and alcoholic sprees. One month before his admission to the hospital, on March 11, 1931, severe tonsillitis and cervical adenitis developed and lasted for a week. After a brief asymptomatic interval rapidly migratory articular pains and swellings associated with a fine purpuric eruption appeared. The following week he had diffuse abdominal pain and persistent constipation. The temperature ranged about 103 F. Abdominal pain was not entirely new, having been associated with drinking bouts.

At the initial examination the patient lay guardedly, complaining of pain in the hypogastrium, knees and hips. The heart showed slight enlargement, an apical systolic murmur with diffusion over the left precordial region, a ringing second pulmonary sound, blurred sounds and a suggestion of a pericardial friction

10. Eppinger, cited by Gruber.[9]

11. Dietrich, K.: "Periarteritis Nodosa" der Haut des Vorderarmes nach Erysipelen derselben, Ztschr. f. Kreislaufforsch. **25**:305, 1933.

12. Harris and Friedreich, cited by Gruber.[9]

13. Klotz, O.: Periarteritis Nodosa, J. M. Research **37**:1, 1917.

14. Some of the necropsy material has been reported in other papers from the hospital in different connections (cases 1, 5, 6, 8, 10, 11 and 17).

15. Dr. Margot Freund gave permission for the use of these case reports.

rub. The distention was severe, the hypogastric pain was inconstant and the tenderness was relatively slight. Effusion and tenderness of the knee joints were noted. A slightly raised, finely purpuric rash with barely perceptible erythematous papulomacules was distributed over the flexor surface of the thighs, insteps, lower costal margin on the right side posteriorly and right buttock.

At this time the blood pressure was 140 systolic and 74 diastolic. The blood count showed: hemoglobin, 86 per cent; leukocytes, 17,000; polymorphonuclear leukocytes, 90 per cent, and platelets, 480,000. The urine contained albumin, red blood cells and casts. There was no occult blood in the stools.

The initial diagnosis was erythema, with visceral, rheumatoid and perhaps cardiac manifestations.

Because of severe constipation, abdominal cramps and distention, an acute surgical abdominal condition was considered to exist, perhaps due to a gangrenous appendix. At operation retroperitoneal edema of the appendical bed and partial obliteration of the appendix were present; they were thought insufficient to account for the antecedent clinical course. Microscopic examination showed multiple foci of necrotizing arteritis in all phases and subacute inflammation of the appendical wall. The diagnosis of periarteritis nodosa was thus established by operation, and further manifestations were awaited.

The subsequent course was characterized by persistent distention, ileus, remittent fever and inanition. The urea nitrogen content of the blood fluctuated about 50 mg. per hundred cubic centimeters. The urinary findings remained unchanged. The blood pressure rose in one month to the level of 160 systolic and 110 diastolic. The hemoglobin content decreased to about 50 per cent, and the leukocytosis rose to 36,000. Pitting edema of the feet gradually appeared. Fleeting precordial pain, vagrant cardiac murmurs and also a transient tripartite rhythm, which was considered equivalent to a pericardial friction rub, were noted. Nodules were not detected in the peripheral blood vessels. The electrocardiogram was normal. Roentgenographic examination showed pneumonia of the lobular type in the lower lobe of the right lung. Death occurred about three months after the onset of tonsillitis.

Postmortem Observations.—The patient died on May 18. Examination revealed macroscopic periarteritis nodosa of the bronchial, coronary, pancreatic, mesenteric, adrenal and cystic arteries; brown induration of the lungs with submiliary nodules and thrombosis without infarction; fibrinous pericarditis; verrucae of the closure line of the mitral valve; hemorrhagic infarctions of the liver associated with obliteration of the arteries, and diffuse gliosis of the brain.

Microscopically there were hyalinization and occasional intimal proliferation of the cerebral arteries; myocardial degeneration, with Aschoff bodies; subacute glomerulonephritis of the intracapillary type; small renal aneurysms, and productive thickening of the meninges.

Summary.—Clinically this patient's condition belonged to the Osler erythema or the Schönlein-Henoch group with abdominal symptoms, for which appendectomy was performed. The lumen of the appendix was obliterated; characteristic lesions of periarteritis nodosa were noted microscopically. The subsequent course was complicated by pericarditis, pulmonary symptoms, renal insufficiency, hypertension, fever and progressive inanition. The postmortem examination showed periarteritic involvement of the lungs, heart, liver, gallbladder and kidneys, fibrinous pericarditis and subacute glomerulonephritis.

CASE 2.—A 6 year old boy was admitted to St. Vincent's Hospital without a previous history of significant illness. The child had had severe abdominal pain for two days without vomiting. The abdomen was diffusely rigid, a systolic murmur was present and the temperature was 102 F. The leukocyte count was 28,000 with 80 per cent polymorphonuclears and rose in two days to 39,000 with 96 per cent polymorphonuclears. Appendectomy was performed, and the lesions of periarteritis nodosa were revealed. Recovery was uneventful.

Summary.—A child with abdominal pain and rigidity, fever and leukocytosis was operated on for appendicitis. Periarteritis nodosa involving the appendix was demonstrated.

CASE 3.—H. B., a 17 year old Jewess, was admitted to the hospital on May 23, 1932. She had apparently been well but for one year of intermittent pain in the right lower quadrant of the abdomen, which was exaggerated only by exertion. Some tenderness on deep pressure over McBurney's point was present. A short presystolic murmur was noted at the apex, with marked reduplication and accentuation of the second pulmonic sound. Laboratory examination revealed no abnormality. A pyelogram showed slight dilatation of the pelvis of the left kidney and some mobility of the right kidney. Nephropexy and appendectomy were performed on the right side; the cecum was congested and the appendix shriveled. Histologic examination of the appendix showed chronic inflammation, with obliteration of the lumen, and many arterioles, with acute necrotizing arteritis as in periarteritis nodosa. On close questioning postoperatively a history of fleeting articular pain was elicited. The convalescence was uneventful except for mild pharyngitis. The patient was discharged from the hospital on June 16. Follow-up examination has shown no subsequent symptoms.

Summary.—A girl, otherwise apparently well, had atypical pain in the right lower quadrant of the abdomen, for which appendectomy and right nephropexy were performed. Necrotizing arteriolitis of the appendix was present. The patient is now apparently well.

CASE 4.—An 8 year old Irish boy was admitted to St. Vincent's Hospital. Nausea, vomiting and abdominal pain had developed three days before, and a diagnosis of appendicitis was made. There was a leukocyte count of 20,000 with 86 per cent polymorphonuclear cells, together with acetonuria. Appendectomy was performed on the same day; the appendix was normal.

Three days later the boy had several convulsions and then complained continuously of pain in the abdomen and in both arms. White blisters appeared on the tongue.

Two blood transfusions were given, and six weeks after admission to the hospital the boy seemed well enough to be out of bed. Transient amaurosis and vagrant pains occurred repeatedly. His face became swollen. The urine contained increasing amounts of albumin, casts and red and white blood cells. No note was made of the blood pressure. The temperature range was from 98 to 103 F. Reddish fluid oozed from the rectum the day of his death.

The postmortem examination showed periarteritis nodosa of the mesenteric arteries, renal arterioles and hepatic arteries in various stages of healing; adhesions in the right pleura; leukocytic infiltrations of the lung without arterial changes; cardiac enlargement; thickening of the anterior cusp of the mitral valve; slight fibrosis of the papillary muscle; initial proliferation of the coronary artery; organizing necrosis of the myocardium; fatty degeneration of the liver;

aneurysm of an artery of the jejunum, with ulceration, and hyalinization of collapsed glomeruli. The general nervous system was not examined.

Summary.—A boy with symptoms interpreted as due to appendicitis was operated on. During convalescence convulsions, transient amaurosis, albuminous urine and sanguineous stools were noted. Hemorrhage from an aneurysm in the jejunum, chronic peritonitis and pleurisy, acute glomerulonephritis and periarteritis nodosa were noted at necropsy.

CASE 5.—Y. S., a 10 year old Jewess, was admitted to the hospital on June 12, 1924. Three weeks before her admission to the hospital the patient had a sore throat and fever followed by pain and swelling in the right ankle. Two weeks later she had diffuse abdominal cramps and vomited. She was sent to the hospital because of a suspicion of acute appendicitis. On the day of admission to the hospital she fainted and was amaurotic. The temperature at that time was 102 F., and the blood pressure was 180 systolic and 124 diastolic, persisting at this level for most of the clinical course. Purpura of the left hip, fundal hemorrhages, perivasculitis of the retina, nuchal rigidity and a Kernig sign were present.

The hemoglobin value was 93 per cent; the initial leukocyte count was 40,000 with 90 per cent polymorphonuclear cells; subsequently it became 12,000. The urine contained albumin, casts and red and white blood cells. The spinal fluid was normal. The terminal urea nitrogen content of the blood was 30 mg. per hundred cubic centimeters.

There were occasional convulsions, and consciousness varied so that at times the patient apparently perceived objects. On June 23 the blood pressure fell, and death occurred.

The diagnosis rested between uremia and encephalitis.

Postmortem examination showed fatty replacement of the thymus; marked enlargement of the intertracheal lymph nodes and moderate hypertrophy of the left ventricle. Along the course of the coronary arteries were glairy, light brown masses connected with the lumen of the vessel. The greater omentum was attached to the intestine by fibrinopurulent exudate. Two irregular ulcers in the small intestine and numerous aneurysms of the mesenteric vessels were noted. No gross aneurysm of the kidneys but numerous yellow wedge-shaped infarctions, corresponding to microscopic occlusions, of the renal arterial supply by periarteritic lesions were present.

Summary.—Following arthritis and an infection of the upper respiratory tract, abdominal symptoms suggestive of acute appendicitis appeared. Soon transient amaurosis, hypertension and symptoms of involvement of the central nervous system developed. At postmortem examination periarteritis nodosa and fibrinopurulent peritonitis were present.

CASE 6.—W. S., a 39 year old Jew, was admitted to the hospital on Sept. 3, 1919. He gave a history of typhus fever and recurrent peritonsillar abscesses. The illness under consideration began with pains in the muscles of the legs, in the right testicle and in the lumbar region. On one occasion hematuria, epigastric pain and fever simulating an acute surgical condition occurred. Vague epigastric tenderness was noted. There was marked inflammation of the tonsils.

The temperature ranged about 102 F. The pain subsided and the leukocyte count varied between 36,000 and 54,000 with 75 per cent polymorphonuclear

cells. The blood pressure was 160 systolic and 90 diastolic. The urea nitrogen content was 35 mg. per hundred cubic centimeters of blood.

A pure culture of Streptococcus haemolyticus was obtained from material from the throat.

All diagnostic approaches having given negative information, the patient was considered to have suppurative retroperitoneal foci behind the omental sac secondary to the pharyngeal infection.

At exploratory laparotomy periarteritis nodosa of the mesenteric vessels, enlargement of the head of the pancreas and an area of fat necrosis in the omentum were noted. Peritoneal cultures were sterile.

Five days postoperatively there was painless hematuria. A diffuse maculopapular rash on the hands and forearms and external nodules appeared. The nodules on the face were pulsatile. Failing vision and a fibrinous exudate on the temporal side of the optic nerve head were noted and a low grade of nephritis.

The patient was discharged slightly improved but was readmitted in two months with generalized edema, dyspnea, urinary signs of nephritis and patchy consolidation of the lungs. The sputum contained pneumococci and streptococci.

All the nodules had disappeared except several hard ones along the temporal and brachial arteries. There was neuroretinitis, and the blood pressure was 104 systolic and 100 diastolic. Bronchopneumonia and uremia developed. Death occurred on October 8.

Postmortem examination revealed periarteritis nodosa and aneurysms of the temporal, brachial, coronary, splenic, gastric, renal, pancreatic and superior mesenteric arteries; thickening of the pleurae at the apexes; lobular pneumonia and anthracosis; hemorrhage in the pericardial sac; congestion of the gastric mucosa; four shallow gastric ulcers on the posterior aspect near the lesser curvature, with hemorrhage extending down to the muscularis; pancreatitis, and perirenal hematoma and perinephritis. No changes were noted in the brain.

Summary.—The patient had myalgias, followed by severe abdominal pain and hematuria, for which an exploratory laparotomy was performed. The diagnosis of periarteritis nodosa was made at that time. Subsequently, painless hematuria, large subcutaneous perivascular nodules and a maculopapular rash on the upper extremities appeared. Death occurred, with uremia, in two months. A perirenal hematoma, gastric ulcers and pancreatitis, in addition to the characteristic vascular lesions, were present.

CASE 7.—M. B., a 38 year old Jew, was admitted to the hospital on Dec. 23, 1931. He had passed a life insurance examination three years before and had had no acute infectious illnesses. Pleural pain developed on the right side a year and a half later, and subsequently there were headaches, dyspnea and nocturia. At this time hypertension was discovered. The symptoms increased, and edema of the ankles appeared. At the time of his admission to the hospital examination of the fundi showed obliterated disk margins, reddened disks, extremely thin arteries, full veins, many exudates and a few hemorrhages. Râles were present at the bases of the lungs, the heart was enlarged to the left and a gallop rhythm was present. The liver was enlarged, and ascites was present.

The blood pressure was 205 systolic and 150 diastolic. The hemoglobin value was 85 per cent. The leukocyte count was 35,000 with 86 per cent polymorphonuclear cells. The venous pressure was 22 cm. of water. An electrocardio-

gram showed left ventricular preponderance, an inverted T_1 wave and low T_2 and T_3 waves, suggestive of poor myocardial function. The urea nitrogen content was 34 mg. per hundred cubic centimeters of blood. The initial examination showed much albumin and some casts in the urine. The diagnosis at that time was the malignant phase of essential hypertension.

Irregular, low grade fever was present and was attributed to bronchopneumonia, probably at the base of the left lung. No roentgen findings were recorded.

Two weeks after admission to the hospital the patient became stuporous and cyanotic and had Cheyne-Stokes respiration. The venous pressure was 14 cm. of water. The urine then contained many red blood cells (a transient finding). Swelling and pain were noted on motion of the right knee. The abdomen remained distended. There was tenderness, particularly in the left lower quadrant of the abdomen. The stools were normal. Sepsis due to pneumococci, with metastases to the knee and peritoneum, was considered to be present, but a blood culture was sterile. Aspiration of the knee and abdomen yielded sterile fluid containing 7,000 white blood cells. The leukocyte count at this time was 16,650 with 81 per cent polymorphonuclear cells.

A pericardial friction rub was present. The neck became rigid, and positive Kernig and Brudzinski signs appeared, but the spinal fluid was normal on two examinations. All symptoms continued unchanged, and severe terminal diarrhea developed. The patient died on Jan. 16, 1932.

Postmortem examination revealed purpura of the antecubital fossa; cardiac enlargement; a necrotic infarct of the lower lobe of the left lung, with fibrinous pleurisy dependent on a fibrosed blood vessel; healed apical tuberculosis of the upper lobe of the left lung; bronchopneumonia of the lower lobes of both lungs; pleural adhesions on the left; fecal peritonitis; hemorrhaghic infarcts of the small intestine, with one perforation in the jejunum; small punctate purpuric, occasionally ulcerated lesions of the mucosa of the large intestine; infarcts of the liver and pancreas secondary to fibrosed or necrotic arterioles; finely granular kidneys, mottled by tiny confluent depressed punctate red areas; necrotizing ureteritis, and edema of the brain.

Microscopically, necrotizing arteritis of the small coronary branches and a large parietal thrombus of one coronary artery were noted. The outstanding lesion in the kidneys was the severe intimal thickening of the entire arterial tree, which was loosely cellular and without much hyalinization. The renal parenchyma showed focal atrophy with an increased amount of stroma and vascularization and frequent fibrotic glomeruli without capsular exudate or an increased number of nuclei. The renal picture was that of nephrosclerosis lenta progressa. There was thickening of the cerebral vessels with perivascular gitter cells and diffuse gliosis.

Summary.—After hypertension, neuroretinitis and cardiac insufficiency of about a year's duration the patient showed nuchal rigidity, bloody urine, diarrhea, swelling of the right knee and abdominal tenderness. Clinically he appeared to suffer from malignant sclerosis. At necropsy, in addition to malignant nephrosclerosis, periarteritis nodosa was present, with secondary ulcerations of the small intestine, hepatic infarcts and necrotizing ureteritis.

Case 8.—A. V., a 10 year old Jewess, was admitted to the hospital on Feb. 27, 1931. Seven weeks before her admission to the hospital the child had mild, atypical scarlet fever, after which desquamation was profuse. A Dick test was

negative. The next week urticaria developed and persisted for about a month, accompanied with a temperature ranging up to 104.4 F. During this time she complained occasionally of articular pains, especially in the small joints of the hand.

The urine was normal, except on one occasion, when a great deal of albumin was present for only one day. The blood count and electrocardiogram were normal. The blood culture was sterile.

Generalized violent abdominal pain and rigidity developed three days before the patient's admission to the hospital. Tenderness was especially marked over the right upper quadrant of the abdomen. The leukocyte count then was 14,000, with 79 per cent polymorphonuclear cells. Exploratory laparotomy was performed for an intra-abdominal suppurative condition. There was marked intestinal distention. The appendix was normal. A fine, fibrinous exudate extended across the under-surface of the liver. The gastrohepatic ligament was edematous throughout its entire length, and there were many fine periduodenal adhesions. There was no pus.

Three days postoperatively bilateral bronchopneumonia developed, involving chiefly the lower lobe of the right lung. The leukocyte count ranged about 25,000 with 80 per cent polymorphonuclear cells; the platelet counts were 450,000 and 380,000. There was mild progressive anemia.

In spite of several transfusions the child's condition remained poor, and the temperature was unchanged. About three weeks after her admission to the hospital a coarse pleural friction rub was noted in the lower portion of the left axilla, and that area became tender and dull. The condition remained unchanged for about ten days. The liver and subphrenic space were explored by means of aspiration without revealing any positive signs.

During this time a distinct, loud systolic murmur had appeared, which varied in intensity and was transmitted toward the axilla. There were also occasional transitory murmurs at the base. It was concluded that a pericardial effusion might be present. Large doses of salicylates were given. The temperature was depressed for a few days, but the child became almost pulseless. When the salicylates were stopped, the condition of the pulse improved temporarily. The child died of heart failure on April 19. Postmortem examination revealed marked pulmonary congestion; acute verrucous lesions of the mitral valve; moderate cardiac enlargement; fresh Aschoff bodies; a complicating lesion of one of the myocardial arteries—disappearance of the elastica interna, fibrosis of the media, marked thickening of the intima and perivascular fibrosis; renal infarcts dependent on periarteritis nodosa of the interlobular arteries; diffusely distributed purpuric spots on the visceral pleura, the peritoneal covering of the entire gastro-intestinal tract and the mesentery, and pleural, perihepatic and perisplenic adhesions.

Summary.—The patient presented the sequence of atypical scarlet fever, urticaria and articular pains and finally showed symptoms suggesting intra-abdominal suppuration within a period of two months. At laparotomy the only abnormalities were edema of the gastrohepatic ligament and adjacent fresh adhesions. Fever persisted, and a systolic murmur and pericardial friction rub developed. There was no response to salicylate therapy. Death was due to heart failure. Postmortem examination showed lesions of rheumatic fever, periarteritis nodosa of the kidneys and polyserositis.

CASE 9.—H. L., a 50 year old Jew, was admitted to the hospital on Aug. 25, 1930. Three months before his admission violent epigastric pain had developed, attributed to ulcer or cholecystitis, and had lasted for ten days. The patient had stuttering speech for one day. Pain in one leg, nocturia, polydipsia and repeated vomiting then occurred and lasted for about three weeks. On the day of admission to the hospital the patient had a sudden, violent headache, followed by sudden complete blindness; gradually the pupils were fixed to light, and left external strabismus and edema of the retina and disk were present. Pretibial edema and occasionally a pericardial friction rub were noted.

The blood pressure was maintained at about 190 systolic and 120 diastolic. The hemoglobin content was 66 per cent. The leukocyte count was 12,000 with 94 per cent polymorphonuclear cells. The urine contained much albumin and no red blood cells. This finding was considered indicative of glomerulonephritis rather than the malignant phase of essential hypertension. The urea nitrogen content of the blood was 100 mg. per hundred cubic centimeters. The spinal fluid was normal.

The original stupor deepened, and death occurred, with the patient suffering from uremia, on September 8.

Postmortem examination revealed periarteritis nodosa of the gastric arteries; small renal aneurysms; recanalization of the hepatic arterioles; hyalinized splenic arterioles; thickened pulmonary arterioles; adhesive pleurisy; bronchopneumonia; universal adhesive pericarditis, with calcification over the right ventricle; slight cardiac hypertrophy; an increased amount of connective tissue in the portal canals, and renal infarctions secondary to aneurysms ("the kidneys had marked atrophy with markedly decreased function of the parenchyma, more than would be expected from the gross appearance"). No changes were noted in the central nervous system.

Summary.—An elderly man with epigastric pain and hypertension presented the clinical picture of glomerulonephritis and died in uremia. Postmortem examination revealed periarteritis nodosa, with healed lesions involving principally the kidneys, stomach and liver.

CASE 10.—R. S., a 7 year old Jewish boy, was admitted to the hospital on March 20, 1931. There was a history of whooping cough, measles, chickenpox, mumps and infrequent colds. There had not been any suggestion of a rheumatic state. Two months previously he had a mild attack of scarlet fever, with desquamation occurring within two weeks. Fever, cervical adenitis and frequent epigastric cramps developed. The following week, after the cessation of these symptoms, there was migratory pain in the ball of the right foot, right thumb and groin unassociated with any local signs, and finally pain developed in the scrotum.

Dyspnea and pallor were noted for the first time two weeks before his admission to the hospital, when a diagnosis of rheumatic carditis was made though no other cardiovascular findings were then present.

The child was of the so-called pituitary habitus and the size of a 14 year old child. The heart was noted to be enlarged, the liver was palpable and the diagnosis of rheumatic fever was concurred in. On roentgen examination the left ventricle was enlarged, and the lungs were diffusely mottled, the interpretation being mitral disease with pulmonary congestion.

The hemoglobin content was 38 per cent. The leukocyte count was 16,000 with 81 per cent polymorphonuclear cells. All the laboratory tests gave normal results Fever persisted, the temperature occasionally reaching 105 F.

Digitalis and salicylates were given. The general condition became worse, and death due to cardiac insufficiency occurred on April 10.

Postmortem examination revealed miliary nodules related to the pulmonary arteries, a nodular coronary artery, a flabby myocardium, subacute verrucous rheumatic endocarditis of the mitral valve, a MacCallum lesion of the left auricle, thickened intrarenal arteries, granular deposits in the pleura, collapse of the lower lobe of the right lung, thickened pulmonary arteries and exudate—free bronchi.

Microscopically, acute periarteritis nodosa of the renal arterioles, parietal venous thrombi in the kidneys and lungs, recanalized arteritic lesions in the liver and heart and Aschoff bodies were noted.

Summary.—A child of the Fröhlich habitus had a mild attack of scarlet fever followed by epigastric cramps and articular pains. The subsequent clinical course and findings suggested acute rheumatic fever. Typical lesions of rheumatic fever and of periarteritis nodosa with some healing were present at necropsy.

Case 11.—S. M., a 10 year old American-born Italian boy, was admitted to the hospital on Oct. 2, 1923. Previously he had been well. For the past ten weeks he had had shooting pains in the extremities and trunk, generalized hyperesthesia and a temperature of 103 F.

Examination revealed pharyngitis, a palpable spleen, left ankle clonus and a pseudo Babinski sign. The diagnosis at that time was polyneuritis or polymyositis. The hemoglobin content was 85 per cent, and the leukocyte count, 14,000 with 80 per cent polymorphonuclears. The bleeding time and platelet count were normal. Several blood cultures were sterile.

Purpuric spots appeared soon on the back and in the pectoral region, and a positive tourniquet test was obtained. One swelling appeared along the outer aspect of the left humerus and several along the deltoid muscles and seemed to involve the periosteum.

Precordial pain developed, and hypertension increased, the pressure rising from 145 systolic and 112 diastolic to 176 systolic and 138 diastolic in several months. Finally there was clinical cardiac enlargement.

A biopsy specimen of muscle was taken, and dilated vessels with perivascular infiltration by polymorphonuclear leukocytes was noted. A flexor contracture developed. Gradually numbness in the left hand, ankle clonus, convulsions, nuchal rigidity, myoclonus and spontaneous hippus movements were noted. The fundi showed temporal exudate. At this time the spinal fluid contained 1,280 polymorphonuclear cells per cubic centimeter. There was no retention of urea nitrogen, and the urine was normal. The hematologic condition did not vary much throughout the entire course. The diagnosis then considered was a vascular lesion in the region of the midbrain or quadrigeminal plate, with meningitic and encephalitic phenomena. There was gradual improvement from the semiconsciousness into which the patient had lapsed to a state of deteriorated sensorium. Some ocular signs persisted. There was recurrent infection of the upper respiratory tract, and the left testicle became swollen. Death due to pneumonia occurred on March 27, 1924.

Postmortem examination revealed brown induration of the lungs; porphyry-like kidneys with thickened interlobular arteries and some periarteritis nodosa; focal degeneration of the renal parenchyma and calcium deposits in the tubules; round cell infiltration of the periportal spaces, one periarteritis nodule of the adrenal gland; periarteritis nodosa of the muscles; pea-sized, sacculated aneurysms

of the coronary, gastric and gastric serosal arteries and miliary aneurysm formation in the pancreas; thickened hepatic and cystic arteries without aneurysms, and complete occlusion of one intrahepatic artery by thrombosis associated with periarteritis nodosa.

Summary.—An Italian boy had had generalized pain in the muscles, fever and pharyngitis for eight months. Persistent hypertension and encephalomeningitic symptoms developed. Extensively distributed periarteritis nodosa was present at necropsy.

CASE 12.—J. S., a 51 year old Dutchman, was admitted to the hospital on Jan. 16, 1931. The patient's first complaint was of parosmia six weeks previously. The right antrum was irrigated three weeks later, and two days after this procedure pain and inflammatory swelling of the right periorbital tissues appeared. Soon peripheral paralysis of the right facial nerve and complete nerve deafness on the right developed. No otitic discharge was present. The patient then complained of pain in the throat, dysphagia and tenderness of the anterior portion of the neck. Finally, on the day before his admission to the hospital, a red, painful swelling, about 5 cm. in diameter, was noted in the region of the right malleolus.

Examination, in addition to the foregoing findings, revealed severe wasting, particularly of the muscles, emphysema and bronchitis. Tenderness over the sacrum and edema of the glottis were present. The right ear drum was thickened, gray and retracted. Taste was impaired on the right anterior portion of the tongue. Edema of the eyelids and chemosis of the left conjunctiva, episcleritis and iritis ensued. The fundi were normal.

The urine was normal. The Wassermann reaction of the blood and spinal fluid was negative. The leukocyte count was 18,400 with 85 per cent polymorphonuclear cells.

As the periorbital swelling subsided and the general condition appeared better, therapy for the condition of the sinuses was begun. The temperature, which had been normal, fluctuated regularly between 99 and 102 F. Cultures of pus removed from the right antrum on two occasions contained Staphylococcus aureus and Staphylococcus albus. The condition was considered to be due to chronic sepsis, with the focus probably in the sinuses. From time to time the patient complained of vagrant pain and tenderness in the right knee, the right epididymis, the sacrum and the left ear. Some impairment of hearing on the left and vesiculation of the posterior wall of the left canal were found. In three days this condition had progressed so that there were peripheral paralysis of the left facial nerve and complete deafness in the left ear, attributed to a lesion in the left geniculate ganglion.

The urine became grossly bloody about three months after the patient's admission to the hospital. There was no renal tenderness or enlargement. The possibility of periarteritis nodosa was suggested by the urologic consultant, Dr. Beer. The blood picture had changed; the leukocyte count was 12,000 with 38 per cent monocytes, suggesting monocytic leukemia in response to infection. The hemoglobin value had fallen, and several transfusions were given. There was no improvement, and the urine continued to be bloody. The patient became comatose, tremors of the upper extremities developed and death occurred on April 10.

Postmortem examination revealed periarteritis nodosa of the kidneys, testicles, heart and mesenteric arteries; brown, turbid, purulent material in the right antrum; chronic emphysema and chronic bronchitis; dilatation of the right ventricle and

parenchymatous degeneration of the myocardium; acute diffuse pancreatitis (normal ducts) and occasional hyalinization of the arterioles; splenic enlargement, with hemorrhagic foci, a few follicles, many large mononuclear cells, many colonies of cocci without polymorphonuclear reaction, foci of fibrosis and arteriolar hyalinization without arteritis; numerous anerysms of the kidneys, with rupture of one into the left renal pelvis; compression of the renal parenchyma in the region of the aneurysms, occasional hyalinized glomeruli and arterioles, and moderate enlargement of the cerebral ventricles. A study of the brain was not completed. The bone marrow was normal.

Summary.—Following maxillary sinusitis, there developed, in sequence, deafness, erythematous swellings on the extremities and vagrant tenderness, a Ramsay-Hunt syndrome of the left geniculate ganglion and hematuria. Because of the heterogeneity of the symptoms the diagnosis of periarteritis nodosa was suggested. The blood count was suggestive of monocytic leukemia. Lesions of periarteritis nodosa with rupture of an aneurysm into the renal pelvis were noted at necropsy.

CASE 13.—J. G., a 50 year old Jew, was admitted to the hospital on Aug. 18, 1928. He had had Pott's disease and pleurisy in childhood. He had been well until three weeks before admission to the hospital. At that time he suffered from acute antral sinusitis, and a nasal operation was performed. In the hospital the eyes were noted as being prominent and suffused, and a cavernous sinus thrombosis was suspected. The temperature was 104 F.; the leukocyte count ranged about 19,000 with 90 per cent polymorphonuclear cells. The urine contained casts and red and white blood cells. A diagnosis of bacteremia with a primary focus in the sinuses and possibly associated nephritis was made. Pain developed in the right elbow and left shoulder, and there was also bloody expectoration.

Ulcerations appeared on the tongue and buccal mucosa. Hemorrhagic cutaneous lesions, considered as a toxic manifestation secondary to miliary tuberculosis, appeared. However, the lingual lesions disappeared more rapidly than could be accounted for on the basis of tuberculosis. A rash, consisting of purpuric lesions, appeared. The lesions changed to fawn-colored maculopapules from several millimeters to several centimeters in diameter; these faded on pressure. They were of generalized distribution but most numerous on the neck and trunk. They were considered as erythema multiforme in the course of tuberculosis.

The sputum had shown tubercle bacilli on two occasions. A roentgenogram of the chest made a week after the patient's admission to the hospital showed no evidence of tuberculosis, but in two weeks small nodular infiltrations were noted in the apex of the right lung.

Cystoscopy was performed because of the urinary findings and disclosed obstruction of the left ureter.

Fever was present throughout. Blood cultures were sterile. The pressure and the urea nitrogen content of the blood were normal.

Postmortem examination revealed kyphoscoliosis; hemorrhagic spots on the dorsa of the hands and forearms, thighs, knees and abdomen; perioral herpes; necrotizing tracheobronchitis and calcification of the tracheobronchial lymph nodes; pulmonary nodules; small hemorrhages, infarcts and perivascular thickening of the small vessels of the kidneys; a calculus in the left kidney, and periarteritis nodosa of the ileum.

Microscopically there were endarteritis of the coronary arteries; peribronchial infiltration; periarteritis nodosa of the pulmonary arterioles; focal necrosis and periportal fibrosis of the liver with perivascular infiltration and fibrinoid changes in the intima, and periarterial infiltration of the mesenteric, gastric and small cutaneous arteries.

Staph. aureus and Staph. albus but no tubercule bacilli were cultivated from material from the lung.

Summary.—In a man of 50 with sinusitis, for which an operation had been performed, articular pains, bloody expectoration, oral ulcerations, cutaneous hemorrhagic lesions and nephritis accompanied with fever developed. These were considered a reactivation and dissemination of tuberculosis. Postmortem examination revealed old tuberculous pleurisy and periarteritis nodosa.

Case 14.—S. A., a 72 year old Jew, was admitted to the hospital on Jan. 25, 1931. Previously he had had typhoid (sixty years before), arthritis of the right shoulder (fifteen years before) and, in the past two years, dyspnea on exertion, intermittent claudication and slight nocturia. Six months before his admission to the hospital he suffered a sudden sticking pain in the left lower portion of the chest which radiated into the abdomen and was aggravated by respiration. It was followed by a duller pain, which lasted for a week and was superseded by a sharp, colicky pain in the epigastrium which radiated into the right upper quadrant of the abdomen and into the back. The stools became light yellow and the urine dark. There was nonpruritic jaundice. The pain continued intermittently for about a month, and the jaundice and associated findings improved. There was a loss of 15 pounds (7 Kg.) in this period.

In addition to slight icterus, the initial physical examination showed disseminated purpuric lesions on the skin, generalized cardiac enlargement, extrasystoles, ascites, slight enlargement of the liver, and slight pitting edema over both ankles. Examination of the fundi revealed the arteries to be somewhat thin and irregular, with indentation of the veins.

The hemoglobin value was 90 per cent, and the leukocyte count, 10,700, with 90 per cent polymorphonuclears. The icteric index was 55. The blood pressure was 145 systolic and 80 diastolic. The bleeding, clotting and clot retraction time were normal. The stools contained no blood; urobilin was present. Abdominal puncture yielded a serohemorrhagic fluid, with 70 per cent polymorphonuclear leukocytes. The Wassermann test of the blood was negative. The blood sugar content was 115 mg. per hundred cubic centimeters. The urea nitrogen content at the time of the patient's admission to the hospital was 81 mg., and it rose finally to 166 mg. The urine contained a moderate amount of albumin, bile and urobilin but no cells or casts. The electrocardiogram showed preponderance of the left ventricle.

The icterus receded, but the patient's general condition became worse. The temperature varied from subfebrile to subnormal. He became drowsy, and vomiting, some muscular twitchings and tenderness high in the abdomen were noted. He died on January 30. He was considered to have a malignant growth with metastases to the liver.

Postmortem examination revealed slight icterus; disseminated, irregularly confluent bluish red lesions in the groins and axillae; serous peritoneal fluid; obliterating adhesions of the right pleural cavity; fibrinous granules of parietal pericardium at the base of the heart; fresh adhesions over the great vessels; fibrinous exudate over the auricles; moderate brown induration of the lungs;

gangrene of the right auricle; subendocardial hemorrhage of the left papillary muscle; thickened, occasionally thrombotic arterioles of the liver; one periarteritic nodule of the gallbladder; one patch of necrosis in the pancreas; petechial and linear hemorrhages and hemorrhagic cysts of the kidneys; esophagitis, with lesions resembling those of the skin, and diffuse hemorrhage of the gastric, jejunal and ileal mucosa.

Microscopically there were noted hyalinization of many glomeruli, with some anemic and some congested glomeruli and some partially necrotic glomeruli without inflammatory reaction; hyalinization of the arterioles, intimal thickening of the interlobular arteries and some focal necrotizing arteritis with adventitial infiltration; acute necrosis and hemorrhage of the entire right auricle; fibrosing arteritic lesions of a definite inflammatory type, with narrowing of the lumen of the coronary arteries; hemorrhages with arteritis of the gastro-intestinal tract; acute necrotizing arteritic lesions with polymorphonuclear leukocytic infiltration of the liver; acute inflammation of the periportal spaces and polymorphonuclear leukocytes and bile thrombi within the small bile ducts; typical acute arteritic lesions and congested capillaries involving the gallbladder; healed arteritis of the pancreas, and small foci of necrosis with hemorrhagic and acute arteritis of the adrenal glands.

Summary.—In an aged man with symptoms of moderate cardiac insufficiency pain suddenly developed in the epigastrium and in the lower left portion of the chest, followed by moderate icterus and was attributed to a metastatic malignant condition of the liver. He died in uremia. Necropsy revealed polyserositis, periarteritis nodosa, gangrene of the right auricle and arteriolitis of the kidneys.

CASE 15.—J. B., a 30 year old British West Indies Negress, was admitted to the hospital on Aug. 6, 1933. This patient had spent most of her life in the United States. She had had a febrile illness associated with puffiness of the eyelids and two attacks of rheumatic fever in girlhood. She had since been well except for mild cardiovascular symptoms and constipation until one month before her admission to the hospital. There was a family history of hypertension.

The presenting symptoms developed rapidly: violent headaches, blurring of vision, nocturia, intermittent hematuria, dysuria, precordial pain, palpitation, dyspnea, orthopnea, nausea, vomiting and abdominal pain. She had pain in the right anterior portion of the chest and cough productive of mucus and occasional flecks of blood for three days. She became increasingly drowsy. The eyelids were puffy.

At the time of her admission to the hospital the patient was twitching, and her breath was urinous. The fundi showed papillitis, destruction of the disk markings, linear hemorrhages, old retinal exudates and narrow, irregular arteries.

The heart was generally enlarged, and a long, blowing diastolic murmur was heard, best at the apex, where there also was a gallop rhythm. The pulmonic and aortic second sounds were duplicated.

There was bilateral costovertebral tenderness due to shock, and slight tenderness was noted in both lower quadrants of the abdomen.

The blood pressure was 206 systolic and 146 diastolic, the hemoglobin content 45 per cent and the leukocyte count 9,500 with 80 per cent polymorphonuclear cells. The urea nitrogen content was 115 mg. per hundred cubic centimeters of blood. The urine was of low specific gravity and contained much albumin and many red and white blood cells.

The patient was considered to have chronic cardiovascular disease of rheumatic etiology, with uremia on the basis of either chronic glomerulonephritis or malignant sclerosis.

Shortly after the patient's admission to the hospital pulmonary edema developed. An electrocardiogram at this time showed an inverted T wave and marked left ventricular preponderance. Disease of the coronary arteries was considered to be present. There was no response to therapy.

Postmortem examination revealed malignant nephrosclerosis, generalized arteriosclerosis, hypertrophy of both ventricles, partial obliteration of the coronary arteries, hemorrhagic gastritis, ileitis with ulcerations, cystitis, vascular lesions of the wall of the gallbladder and periarteritis nodosa of the stomach, intestines, gallbladder and adrenal glands.

Summary.—A Negress, with a previous history of rheumatic fever, showed symptoms of mild cardiac insufficiency about one month before her admission to the hospital and finally hypertension and uremia. Malignant nephrosclerosis, periarteritis nodosa and hemorrhagic lesions of the gastro-intestinal tract were present at necropsy.

CASE 16.—S. W., a 37 year old Jewish baker, was admitted to the hospital on June 26, 1933. He had been asthmatic for two years and had been found to be sensitive to feathers, wheat, flour and barley. Operations on the nose and sinuses and tonsillectomy had been followed by slight improvement in the symptoms. No hay fever or urticaria had been present. There was no history suggestive of any other chronic illness. He had lost about 50 pounds (22 Kg.).

About seven weeks before his admission to the hospital a pustular, occasionally sanguineous rash appeared over his face and was attributed to some unidentified medication. Sharp, continuous pains and weakness and stiffness of the right hand then developed. About five weeks later watery diarrhea, tenesmus and periumbilical cramps set in. The stool on occasion was purulent and frankly bloody.

At the initial examination the patient seemed cachectic, acutely ill and in asthmatic dyspnea. White-centered petechiae were present on the conjunctiva, the soft palate and the shoulders and arms. Multiple erythematous macules were distributed over the face. A polypoid mass was palpable in the rectum. The extremities were wasted. The right hand was pale and swollen, and there was glovelike hypesthesia. Right ankle clonus was present. No other positive neurologic signs were elicited. There was tenderness over the sacrum, the lower cervical portion of the spine, the sternum and the left ninth and tenth ribs. The fundi were normal.

On sigmoidoscopy an atypical ulcerating lesion was observed, which on biopsy was considered to be of a nonspecific inflammatory type.

The diagnosis, also suggested by roentgen examination, was an ulcerative lesion of the rectum, either nonspecific or due to emebic colitis associated with purpuric manifestations and peripheral neuritis due to avitaminosis or nutritional deficiency.

The blood picture, temperature and neuritis remained unchanged for about two months. A confluent petechial eruption appeared over the right iliac crest. It was considered a toxicoderma of an erythema multiforme type. Diarrhea persisted, with the occasional appearance of occult blood in the stool. Gastrointestinal roentgenograms became negative. Roentgenograms of the chest showed coarse infiltrations in the lower lobe of the left lung, suggesting resolving pneumonia.

Edema of the ankles and eyelids appeared, that involving the eyelids being strikingly localized and nonpitting.

A period of remission followed in which the abdominal pain, diarrhea, fever and leukocytosis disappeared. A barium sulfate enema revealed no abnormality. There was no significant change in the patient's general condition after a transfusion was given.

On August 14, in this period of apparent improvement, there suddenly occurred severe abdominal pain, with rigidity, tenderness and obliteration of the hepatic dulness. Bloody mucoid sputum was expectorated. The diagnosis was generalized peritonitis secondary to a perforated viscus. Death occurred in several hours.

Postmortem examination revealed an erythematous maculopapular eruption on the forehead and cheeks; edema of the ankles and eyelids; generalized cardiac hypertrophy and dilatation; diffuse myocardial fibrosis and focal areas of subacute myomalacia cordis; parietal thrombosis of the right and left ventricles; thrombosis of the left auricular appendage; thrombosis of the small branches of the pulmonary artery of the lower lobes with multiple infarctions; serosanguineous fibrinous pleurisy on the left and hydrothorax on the right; a chronic callous peptic ulcer, with perforation and fibrinopurulent peritonitis; multiple gastric erosions and a small peptic (unperforated) ulcer; multiple anemic infarctions and scarring of the kidneys, and periarteritis nodosa of the heart, lungs, kidney, mesentery, gallbladder, testes and stomach.

Summary.—A man who had had asthma and proved sensitivity, which appeared for the first time two years before his admission to the hospital, became ill with peripheral neuritis and ulcerative colitis. During a remission a perforated gastric ulcer suddenly developed, and death followed. At necropsy periarteritis nodosa, a perforated gastric ulcer, peritonitis and multiple gastric erosions were present.

Case 17.—M. K., a 19 year old woman, was admitted to the hospital on June 4, 1928. She had had frequent attacks of tonsillitis in childhood. Six months before her admission to the hospital she had articular pains, followed by abdominal pain and vomiting for five weeks. Appendicitis and intestinal obstruction were diagnosed, and an appendectomy was performed. Subacute catarrhal appendicitis was present. There was a remission of the symptoms for four months. Symptoms of cardiac insufficiency and also albuminuria, pleural effusion and fever then developed. When admitted to the hospital the patient was in collapse, the heart sounds were distant and a pericardial friction rub was present. The lungs showed signs of fluid and of superjacent compression. The blood pressure was 98 systolic and 70 diastolic, the hemoglobin value 52 per cent and the leukocyte count 10,200. The urine contained albumin (four plus), casts and white blood cells. The urea nitrogen content was 41 mg. per hundred cubic centimeters of blood. The temperature ranged between 98 and 104 F., and the pulse rate was about 120.

Signs of recurrent pleurisy appeared, though no fluid was obtained on aspiration. The face became puffy and the throat red, and pains were noted in the right costovertebral angle and in the large joints. Bilateral ulnar neuritis and an urticarial lesion of the hypothenar process appeared. In the course of the next four months the blood pressure rose gradually to 150 systolic and 116 diastolic, the urea nitrogen content was 77 mg. per hundred cubic centimeters of blood, the urine contained red blood cells and the hemoglobin content fell to 35 per cent, with only a transient response to a transfusion of blood.

Abdominal pain which was not controlled by codeine again appeared. On October 8 death occurred with the patient in uremia. Blood cultures had been sterile. The clinical diagnosis was the indeterminate type of bacterial endocarditis and acute arteritis. (The changing clinical and roentgenographic pulmonary findings are described in the text.)

Postmortem examination revealed generalized, irregular, fine, discrete, purple hemorrhages the size of a pinhead involving the skin and the aponeurotic layer of the scalp; chronic fibrinous pleurisy and pleurisy with effusion; bullous edema of the visceral and diaphragmatic pleura; wedge-shaped hemorrhages in the lungs; no changes in the pulmonary vessels; adhesive pericarditis with sacculated spaces between the apposing surfaces; edema of the surface and base of the heart associated with fresh hemorrhages; focal myocarditis; subacute verrucous endocarditis of the mitral and aortic valves; arteritis of the small arterioles; peritoneal effusion; fatty degeneration of the liver, with a thickened capsule; circumscribed areas of hemorrhage and of superficial ulceration of the mucosa of the stomach near the lesser curvature and on the posterior surface; anemic infarcts of the spleen; necrosis of the pancreas; thickening and edema of the capsule of the left kidney; numerous flame-shaped hemorrhages of the renal parenchyma; one thrombosed vein at the pyelovenous angle of a calyx; gelatinous edematous exudate beneath the pia-arachnoid, and moderate congestion of the cerebral vessels.

Vegetation from the aortic and mitral valves contained gram-positive cocci overgrown by colon bacilli.

Microscopically there were panarteritis and focal periarteritis of the stomach and mesentery; several areas of hemorrhage and necrosis in the medulla, focal proliferation of the nuclei of some glomeruli, slight interstitial fibrosis, and foci of necrotizing arteritis with slight periarteritis; hyaline changes in the vessels, perivascular infiltration with glia cells and fibrosis and occasional pigment-laden gitter cells in the perivascular spaces.

Summary.—A patient with recurrent tonsillitis was ill for about a year with articular pains, abdominal pain (for which appendectomy was performed), pleural and pericardial effusions, renal insufficiency, progressive anemia and hypertension. The clinical diagnosis was the indeterminate type of bacterial endocarditis and acute arteritis. This was confirmed at postmortem examination, the arteries being typical of "periarteritis nodosa," involving particularly the heart, kidneys and stomach. A meningeal exudate was present. The endocardial vegetations contained gram-positive cocci.

PRODROMAL ILLNESS AND MODE OF ONSET

Gruber's analysis indicated that this syndrome is superimposed on an infectious or septic state. Other recent observers have reported as follows:

Dietrich: Erysipelas of the forearm of two months' duration
Gray: Posttraumatic cellulitis of the left thigh with inguinal lymphadenopathy
Hampel and Conta: Postdiphtheritic cardiac disease complicated by pulmonary periarteritis nodosa
Lindberg: An infected wound of the foot followed by articular pain and fever lasting for one month and merging with localized pains in the bones
Klotz (second case): Acute rheumatic fever of three years' duration; grip of two months' duration
Herrman: Myalgias
Helpern and Trubek: Gonorrhea
Moolten: Meningococcic meningitis

Seven of our series of 17 patients suffered from known prodromal illness of a banal type, such as acute tonsillitis or acute sinusitis, which merged with symptoms attributable to periarteritis nodosa without an intervening period of good health. Scarlet fever of atypical form occurred in 2 other patients in the two months preceding the appearance of arteritic symptoms. The prodromal illness generally seemed a specific disease entity.

TABLE 1.—*Data on Seventeen Cases of Periarteritis Nodosa*

Case	Remote History	Prodromal Illness	Duration of Symptoms Before Periarteritis Nodosa	Symptoms of Onset of Periarteritis Nodosa
1	Recurrent acute tonsillitis; gonorrhea	Acute tonsillitis	1 month	Abdominal pain; pain in joints
5	.....	Acute tonsillitis; pain in joints	3 weeks	Abdominal pain
6	Typhus; recurrent peritonsillar abscesses	Acute tonsillitis	Coincident	Pain in legs, testicle, abdomen (renal type)
12	.....	Acute sinusitis	6 weeks	Peripheral facial neuritis
13	Pott's disease; pleurisy	Acute sinusitis	3 weeks	Pain in joints; lesions of mucous membrane
17	Recurrent acute tonsillitis	Pain in joints	Several weeks	Abdominal pain
8	.....	Atypical scarlet fever	7 weeks	Abdominal pain
		Urticaria; pain in joints	1 month	
10	.....	Mild scarlet fever; pain in small joints	2 months	Cardiac insufficiency
11	.....	Pain in joints	10 weeks	Precordial pain
16	.....	Asthma; sensitivity to feathers, etc.	2 years	Peripheral neuritis; cutaneous lesions
3	Recurrent pain in joints	.....	.....	Pain in right lower quadrant of abdomen
15	Rheumatic fever (twice); acute nephritis	.....	.....	Abdominal pain; renal and cardiac insufficiency
7	Pleural pain on the right	.....	.....	Abdominal pain; renal and cardiac insufficiency
2, 4	.....	.....	.....	Abdominal pain
9	.....	.....	.....	Abdominal pain; pain in leg
14	Typhoid; arthritis	.....	.....	Pain in abdomen and chest

One patient (case 16) had a two year period of asthma and showed manifest sensitivity to feathers, wheat flour and barley. This is the only ascertained instance in which an undisputedly allergic state was intimately associated with the syndrome of periarteritis nodosa. Lamb's first patient had a two year history of asthma and of associated urticaria. However, specific sensitivity was not demonstrated.

In 2 other cases the remote history revealed illnesses which might have been contributory to periarteritis nodosa; the third patient had fleeting articular pains, and the fifteenth patient had two attacks of rheumatic fever and one of acute nephritis. These factors were not, strictly speaking, prodromal.

After the initial illness had persisted for a variable period, generally for about two months, symptoms of a different type appeared, which,

in retrospect, were those of periarteritis nodosa. In 8 cases there was no known prodromal illness. The mode of onset varied as follows: Eleven patients had abdominal pain. About 5 of these had a closely associated history of articular pain, and 2 others had cardiac and nephritic symptoms. Two had cardiac symptoms and articular pains, and 2 had peripheral neuritis; in 1 of these there were also cutaneous

TABLE 2.—*Cardiac Lesions in Periarteritis Nodosa*

Case	Endocarditis	Myocarditis	Pericarditis	Disease of Coronary Arteries	Other Lesions
1	Verrucae (mitral)	Aschoff bodies	+	Nodules	Enlargement of heart
4	.....	Recent fibrosis and necrosis	..	Intimal proliferation	Enlargement of heart
5	.....	.....	..	Aneurysms	Enlargement of heart
6	.....	.....	..	Aneurysms	Hemorrhage in the pericardial sac
7	.....	.....	+	Microscopic periarteritis nodosa; parietal thrombus of coronary artery	Enlargement of heart
8	Acute verrucae (mitral)	Aschoff bodies	+	Microscopic periarteritis nodosa	Enlargement of heart
9	.....	.....	Adhesive pericarditis; patch of calcification		
10	Subacute verrucous rheumatic endocarditis (mitral); MacCallum lesion of left auricle	Aschoff bodies; myocarditis	.....	Nodule	Enlargement of heart
11	.....	.....	.....	Aneurysm	
12	.....	Parenchymatous degeneration	.....	Nodules	Enlargement of heart
13	.....	.....	.....	Endarteritis	
14	.....	.....	Granular pericarditis; fresh adhesions	Microscopic periarteritis nodosa	Necrosis of right auricle
15	.....	Aschoff bodies			
16	.....	Diffuse fibrosis and myomalacia	.....	Nodules	Enlargement of heart; parietal thrombus of ventricles and left auricle
17	Subacute endocarditis; verrucae (mitral and aortic); large vegetation (mitral and aortic)	Focal myocarditis	Adhesive pericarditis; bullous edema; hemorrhages	Microscopic periarteritis nodosa	Enlargement of heart

lesions and articular pains. Abdominal pain, not adequately explained by involvement of a single organ, was the most usual presenting symptom. One suggestive association was the combination of abdominal pain with apparently irrelevant symptoms, for instance, of arthritis, nephritis or cardiac insufficiency.

The syndrome, for some unknown reason, involves males more frequently than females; in Gruber's series 80 per cent of the patients were male, while the proportion in our much smaller series was 12 males to 5 females. The age range is from infancy to old age. The occur-

rence of periarteritis nodosa in childhood has been the subject of study by Rothstein and Welt.[16]

The known duration of the disease is measured in weeks and occasionally in months. The briefest history is recorded by Thinnes[17] in an infant who was ill for less than a day with acute pharyngitis and apparent abdominal pain before death occurred.

CARDIAC INVOLVEMENT

Varied cardiac lesions were present in all the cases in which a postmortem examination was made. The typical lesions of periarteritis nodosa involved the coronary arteries in 11 of the 15 cases. In 1 of these the condition was complicated by hemorrhage into the pericardial sac secondary to rupture of an aneurysm; in another case necrosis of an auricle occurred owing to the arterial lesion. According to the survey made by Powell and Pritchard,[18] 77 of 150 patients had cardiac lesions directly due to periarteritis nodosa.

Healed periarteritis nodosa, according to Jäger,[19] may terminate in a lesion closely resembling that of arteriosclerosis, particularly in relatively young persons.

Four of our patients showed Aschoff bodies and verrucae of the mitral valve, and 3 of these patients with rheumatic heart disease showed gross periarteritis nodosa of the coronary arteries. Six patients had pericarditis. The third patient, who had a nonfatal, apparently arrested condition, showed clinical signs of mitral stenosis. The relation of the rheumatic state to periarteritis nodosa will be considered in a later section.

Inverted T waves were found in 4 cases of periarteritis nodosa in which repeated electrocardiographic tracings were taken.[20]

The clinical diagnosis of "indeterminate types of verrucous endocarditis and acute arteritis" in case 17 is noteworthy in that it suggests an identity between the condition in some cases of this group and periarteritis nodosa.[21]

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16. Rothstein, J. L., and Welt, S.: Periarteritis Nodosa in Infancy and in Childhood, Am. J. Dis. Child. **45**:1277 (June) 1933.

17. Thinnes, cited by Rothstein and Welt.[16]

18. Powell, R. E., and Pritchard, J. E.: Report of a Case of Periarteritis Nodosa Involving One Kidney, Brit. J. Urol. **4**:317 (Dec.) 1932.

19. Jäger, E.: Zur histologischen Ausheilung der Periarteritis nodosa und deren Beziehung zur juvenilen Atherosclerose, Virchows Arch. f. path. Anat. **288**: 833, 1933.

20. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Diseases, Proc. Soc. Exper. Biol. & Med. **31**:931 (May) 1934.

21. Gross, L.: The Heart in Atypical Verrucous Endocarditis, in Contribution to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 527.

Hypertension was present in 5 patients when they were admitted to the hospital (cases 4, 5, 7, 9 and 15) and was observed in its rapid development during hospitalization in 4 other cases (cases 1, 6, 11 and 17). All but 1 of these patients showed associated abnormal urinary findings, and all of them had renal lesions.

TABLE 3.—*Pulmonary Lesions in Periarteritis Nodosa*

Case	Pulmonary Symptoms	Time	Roentgen Findings	Necropsy Observations of Lungs
	Lesions Directly Dependent on Periarteritic Nodules of Pulmonary Arteries			
1	Slight cough	.....	Lobular pneumonia of lower lobe of right lung	Submiliary nodules; small thrombosed vessels; no infarctions
7	Pleural pain; questionable basal bronchopneumonia of left lung	.....	.....	Necrotic infarctions with pleural fibrin reaction dependent on blood vessel with fibrosed recanalized thrombus
10	.....	.....	Diffusely mottled lungs	Military nodules related to pulmonary arteries
13	Bloody expectoration; tuberculosis ?	.....	Small nodular infiltration of apex of right lung	Necrotizing tracheobronchitis; peribronchial infiltration; nodules; periarteritis nodosa with occlusive thrombi; no caseation
16	Asthma	.....	Coarse infiltrations in lower lobe of left lung suggesting resolving pneumonia	Fibrinous pleurisy on left; hydrothorax on right; periarteritis of lungs with associated infarctions
17	Pleural pain	Early June	On admission, a small pleural effusion at extreme base of left lung; slight general enlargement of heart, probably due to mitral lesion	Mottled, circumscribed hemorrhages; somewhat dilated pulmonary vessels; adhesive pleurisy and effusion
		Middle of June	In 2 weeks, increase in effusion in chest	
		July	In 2 weeks, nearly complete resolution of pneumonia; small effusion at base of left lung	
		August	In 1 month, more effusion of left lung; increase on right side; infiltrations extending out from hilus in region of middle lobe	
		End of August	In 2 weeks, diminution of pleural effusion on left; some evidence of pleural thickening in this region	
	Lesions Associated with Periarteritis Nodosa of Pulmonary Arteries			
16	Terminal bronchopneumonia			Patchy consolidation
8	Bilateral bronchopneumonia; pleural friction rub on left			Pulmonary congestion
9	Bronchopneumonia			
11	Bronchopneumonia			Indurated, brownish lungs
14	Pleural pain on left			Indurated lungs

A systolic murmur was audible in 2 of our cases (2 and 8) and a pericardial friction rub in 4 of our cases (1, 7, 9 and 17) in which pericarditis was present at necropsy. Precordial pain occurred in 3 (cases 1, 11 and 15) and dyspnea in 2 (cases 6 and 10). No case of arrhythmia was recorded.

Incidentally, it may be of diagnostic significance to note that the patients who had rheumatic fever clinically did not respond to treatment with salicylates.

PULMONARY LESIONS

The opinion is current that the lungs are generally exempt from periarteritis nodosa. The first instance of lesions of the pulmonary artery was reported in 1905 by Mönckeberg.[22] Only 4 of Gruber's patients had such involvement. Sternberg reported a fatality due to pulmonary hemorrhage.

Herrman [23] cited the case of a patient with asthma who showed extreme involvement of the small branches of the pulmonary arteries and another with a "cigaret cough" who showed the typical clinical course of periarteritis nodosa, frequent roentgenograms being made. Since his was the first published case in which a roentgenographic study was made, the details will be summarized. Initially the films and the physical signs were normal. In six weeks, while the physical signs remained normal, the roentgenograms showed "diffuse perivascular infiltration spreading out uniformly and equally from both hilar regions." The interpretation was that small infarctions or possibly bronchopneumonia was present. A week later there was "increased confluence indicating further exudation with suggestion of beginning solution or cavitation." In several months there were questionable infarction and effusion. At postmortem examination, in addition to periarteritis nodosa, there were chronic pleuritis and multiple pulmonary infarctions dependent on thrombotic arteries with periarteritis nodosa.

Conta's [24] case was that of a 16 year old boy who had shown postdiphtheritic cardiac symptoms since the age of 4 years. He died of typical heart failure. Roentgenograms showed shadows, ranging in size from that of a lentil to that of a cherry, particularly near the hilus of the right lung, and small pneumonic infiltrations. At necropsy mitral stenosis, adhesions of the right pleura and periarteritis of the pulmonary artery were noted. The heart, liver and kidneys were involved.

Matillon [25] reported a case of periarteritis nodosa in a woman aged 73 with the clinical course of bronchopneumonia.

In Ophüls' [26] patient, who had asthmatic breathing, there were extensive involvement of the small branches of the pulmonary arteries and

22. Mönckeberg, cited by Ceelen, W.: Die Kreislaufstörungen der Lunge, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 3, pt. 3, p. 33.

23. Herrman, W.: Pulmonary Changes in Case of Periarteritis Nodosa, Am. J. Roentgenol. **29**:607 (May) 1933.

24. von Conta: Periarteritis nodosa der Lungengefässe und Lungenröntgenbild, Fortschr. a. d. Geb. d. Röntgenstrahlen **47**:506, 1933.

25. Matillon, B.: La périartérite noueuse, Thèse de Paris, no. 460, 1928.

26. Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**:870 (Dec.) 1923.

also diffuse infiltration of the bronchial tubes and the pulmonary parenchyma with eosinophils.

The foregoing is a fairly comprehensive summary of the reported cases of pulmonary involvement in periarteritis nodosa. Five patients in our series had pulmonary lesions immediately dependent on the typical vascular changes of periarteritis nodosa. In 6 the pulmonary lesions were not of an arteritic type. It is apparent that the exemption of pulmonary arteries and tissue has been exaggerated.

In addition, examination of the accompanying table suggests the following conclusions: 1. Pleural pain is an expression either of primary pleurisy or of pleurisy secondary to extensive pulmonary infarction. 2. The roentgen findings may be suggestive of bronchopneumonia or of a small effusion. 3. The roentgen and postmortem pulmonary observations are more extensive than the clinical findings suggest. 4. The symptoms are variable and though obscure clinically may ultimately be satisfactorily correlated with the type of pulmonary lesion.

RENAL LESIONS

That renal impairment is the most usual accompaniment of periarteritis nodosa has been frequently demonstrated. Arkin [27] listed the incidence as high as 80 per cent; 83 of Gruber's 115 patients had renal lesions. All the patients in our series who were completely examined, including necropsy, had renal involvement. Those in whom no renal disorder was evident are still alive and asymptomatic.

Gruber's analysis showed the following lesions:

	Cases
Renal infarctions	35
Glomerulonephritis	21
Interstitial inflammation	2
Degenerative changes in kidneys	5
	63

In our series of 17 cases the involvement was as follows:

	Total Number of Cases	Urea Nitrogen Retention, Hypertension and Pathologic Urinary Condition, Number of Cases
Renal infarctions and aneurysms	8	4
Acute periarteritis nodosa	2	1
Glomerulonephritis	3	3
Arteriosclerosis	1	1
Malignant sclerosis	2	2
Focal degeneration	1	1
	17	

* In case 17 there were renal infarctions, proliferation of the nuclei of the glomeruli and necrotic arterioles, and the case is entered under the three headings.

Gruber classified the renal changes as passive and active. In the former group are lesions directly dependent on the vascular involvement—thus, infarctions, renal and perirenal hematomas and atrophied

27. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa, Am. J. Path. **6**:401, 1930.

tubules. The active changes are those which presumably were initiated by the factors underlying the periarteritis nodosa and which might be present without accompanying local periarteritis lesions. This is particularly applicable to cases of glomerulonephritis and also to a minor group of cases of interstitial paravascular focal nephritis (Ophüls and Otani [28]).

As was pointed out by Gruber, there is no consistent correlation between the urea nitrogen retention, the hypertension and the abnormal urinary findings and any specific type of renal lesion. These clinical findings may depend on the extent of renal impairment and also on the extent of vascular damage of the entire body. The seventeenth patient had several types of renal lesions, as indicated in the table, and this multiple reaction actually may occur more often than has been supposed.

The majority of our patients showed the anticipated lesions of acute periarteritis, of gross aneurysms and of infarcts secondary to these. It remains to be considered whether the lesions of glomerulonephritis, of malignant sclerosis and of arteriosclerosis of the kidney, which occurred in the other cases, were merely a casual correlation of one vascular disease with another rare vascular disease or whether these too are to be grouped with periarteritis nodosa as mutants in vascular hyperergy. This topic will be discussed in a subsequent section.

Occasionally the renal lesions have required surgical intervention. Retroperitoneal hemorrhage has occurred, and massive hemorrhage from the cortex has been reported by Harris and Friedrichs. Powell and Pritchard [18] published a report of nephrectomy performed for hematuria and suspected renal calculus. The diagnosis was made by examination of the kidney. Myositis developed postoperatively. However, the patient was clinically well for at least a year.

Our sixth patient had gross hematuria at the onset, for which laparotomy was performed, thereby establishing the diagnosis. The thirteenth patient died of renal hemorrhage.

LESIONS OF THE DIGESTIVE ORGANS

It has been frequently stated that the symptoms of periarteritis nodosa mimic acute surgical conditions. The diagnostic dilemma is even more difficult, since grave surgical complications are often present, as illustrated in the following 7 cases in our series:

Case	
4	Ulceration of the jejunum with hemorrhage
5	Ulcer of the small intestine to which the greater omentum was adherent by fibrinopurulent exudate
6	Perirenal hematoma; four gastric ulcers
7	Ulceration of the small intestine and fecal peritonitis
14	Hemorrhagic ulceration of the gastro-intestinal tract
15	Hemorrhagic gastritis and ulcerative ileitis
16	Gastric erosions and ulcers (one perforation)

28. Otani, cited by Gruber.[9]

This incidence of gastro-intestinal ulcer in 15 cases at necropsy is striking. Reported references to this condition are few. As early as 1904 Versé [29] reported a case in which there was rupture of ileal and jejunal ulcers. Gruber's [30] nineteenth patient had a ruptured jejunum. Recently in a child a perforated gastric ulcer and simple ulcers of the pylorus and duodenum were present, all on the basis of periarteritis nodosa. Most bizarre in this connection was case 16, in which there were constantly changing gastro-intestinal symptoms, carefully observed both clinically and roentgenographically under the diagnosis of ulcerative colitis. The one gastric ulcer which had perforated was of the typical callous peptic variety and was definitely associated with the local lesions of periarteritis nodosa.

Periarteritis nodosa undoubtedly is an occasional cause of hemorrhagic pancreatitis, for instance in cases 6, 7 and 15. In case 6 the diagnosis of periarteritis nodosa was established during exploratory laparotomy; at the same time the head of the pancreas was observed to be enlarged, and an area of fat necrosis was present in the omentum. At necropsy several months later the pancreatic vessels were obliterated by thrombi.

In Klotz' second case, that of a 53 year old man, apparently with acute rheumatic fever, death occurred suddenly, and hemoperitoneum involving the gastrocolic omentum and pancreas was present. Three of the patients studied by Gruber had pancreatic lesions—hemorrhage, periarteritic nodules and infarcts. In Lamb's second patient infarcts of the pancreas were present.

Three cases of periarteritis nodosa with involvement of the appendix were observed in this series, and the involvement varied in clinical intensity from very mild to severe. It seems likely that clinically and even pathologically mild involvement, as in cases 2 and 3 (unequivocal (periarteritis nodosa), may occur and escape notice. For instance, Kengyel [31] reported the case of an elderly woman with chronic polyarthritis who had a sudden attack of pain in the right lower quadrant of the abdomen. At laparotomy the ileum was incarcerated. At necropsy there was a healed arteritic process in the intestine; death was attributed to renal insufficiency.

In another case, not included in our series, the lesions of the appendix were slight in comparison to the usual, more foudroyant expression of the syndrome and were of the type called necrotizing arteriolitis,

29. Versé: Periarteriitis nodosa und Arteriitis syphilitica cerebralis, Beitr. z. path. Anat. u. z. allg. Path. **40**:409, 1907.

30. Gruber, G.: Ueber die Pathologie der Periarteritis nodosa, Zentralbl. f. Herz.-u. Gefässkr. **9**:45 (April) 1917.

31. Kengyel: Centralbl. f. allg. Path. u. path. Anat. **53**:137 (Dec.) 1930.

described by Plaut,[32] in appendixes removed in the course of operations for other purposes and in the fallopian tubes. These lacked the gross aneurysms and the extensive anatomic distribution of periarteritis nodosa; an exact identity has not been established. However, the histologic resemblance is important, because it suggests that there may be an attenuated form of periarteritis nodosa.

Hepatic involvement was noted in 70 of a series of 150 recorded cases. The symptoms were icterus and, less frequently, pain in the right upper quadrant of the abdomen. Jaundice occurred in both of Klotz' cases; pain was present in the right upper quadrant of the abdomen in the first case, in which there were extensive thrombosis of the gallbladder, subcapsular hemorrhage, characteristic lesions of the hepatic artery and areas of hepatic necrosis and of lymphocytic infiltration. In his second case purulent material could be expressed from the liver, and there were hepatic and cholecystic arterial thromboses. Most interesting was the fact that portal fibrosis and foci of degeneration of a cirrhotic type were present.

Herrman's patient, studied by MacCallum, also showed lesions of atrophic cirrhosis.

In Ophüls' patient the usual arterial thromboses and secondary infarcted areas were scattered throughout the liver. The unusual feature was the presence of granulomatous nodules.

Kountz'[33] patient had icterus and also peripheral neuritis. The oldest lesions were present both in the arteries and in the veins of the gallbladder. The portal veins of the portion of the liver draining the gallbladder were most involved. It was this association which prompted the author to consider the gallbladder as the original focus in this syndrome with generalized dissemination.

Both of Singer's patients had icterus and pain and tenderness in the right upper quadrant of the abdomen, apparently explained by the periarteritic lesions of the gallbladder (one had cholelithiasis also).

In Gruber's 14 year old patient, with acute nephritis secondary to tonsillar abscesses, microscopic examination disclosed periarteritis nodosa limited to the gallbladder and liver. In another of his patients, with a history of the rheumatic state and grip, the clinical picture of cholecystitis developed. Duodenal drainage disclosed many leukocytes in the bile. Chills and fever occurred, and finally cholecystectomy was performed. On microscopic examination the gallbladder, which was thickened and shrunken, showed periarteritis nodosa. Pass,[34] in a study of infarction of the liver, observed that periarteritis nodosa was the most frequent cause; 22 of 170 cases of periarteritis nodosa were thus

32. Plaut, A.: Proc. New York Path. Soc. **14**:13 (Nov.) 1931.
33. Kountz, W. B.: Periarteritis Nodosa, Arch. Path. **10**:55 (July) 1930.
34. Pass, I.: Infarction of the Liver, Am. J. Path. **11**:503 (May) 1935.

involved. Schmorl's case of acute thrombosis of the portal vein with fatal termination is an example of a severe venous disturbance in the syndrome designated "arteritis."

The foregoing cases are examples of the variety of symptoms and of lesions of hepatic and cholecystic origin on the basis of periarteritis nodosa.

Case	Hepatic Lesions	Original diagnosis
1	Hemorrhagic infarction	
4	Fatty degeneration; periarteritic nodules	
7	Hemorrhagic infarction	
9	Periportal fibrosis	Cholecystitis
13	Focal necrosis	
14	Acute periarteritis nodosa; acute periportal inflammation; polymorphonuclear leukocytes and bile thrombi within small ducts	
17	Fatty degeneration	

In our series such instances have been infrequent. Symptoms suggestive of cholecystitis occurred in case 9. Jaundice was present in case 14, in which the cholangeitis in addition to the hepatic arteritis was noteworthy. Five patients presented arteritic lesions of the liver; 1 showed periportal fibrosis, and 2, fatty degeneration. However, symptoms attributable to hepatic impairment were unusual in these patients. Similarly, though the gallbladder was frequently involved, clinical indications of cholecystic involvement were rare.

Whether the report of cirrhosis of the liver with periarteritis nodosa represents anything more than an accidental association is difficult to say.

LESIONS OF THE ADRENAL GLANDS

Microscopic lesions of periarteritis nodosa were noted in the adrenal glands in cases 14 and 15 without any correlative clinical symptoms.

LESIONS OF THE CENTRAL NERVOUS SYSTEM

Involvement of the central nervous system in this syndrome has been considered rare, though peripheral neuritis was long included as an integral part of periarteritis nodosa and was present in association with the characteristic lesions of the nutrient arteries and occasionally with gliosis of the spinal cord. Twenty of Gruber's patients had peripheral neuritis; 9 had cerebral and meningeal involvement, and 2, lesions of the spinal cord. Hampel [35] reported a case in which the vascular lesions were limited to the meninges. The occurrence of a cerebral hemorrhage in a 10 year old girl with generalized periarteritis nodosa was reported by Kammenstiel. In this case there was the following sequence: otitis media, abdominal pain (for which appendectomy was performed, revealing the appendix to be normal), generalized convulsions and death.

35. Hampel, E.: Zwei ungewöhnliche Fälle von Periarteriitis nodosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:355, 1933.

Bruckmann and Gerlach reported a case in which there were attacks of jacksonian epilepsy, which included unconsciousness and relaxation of the sphincters, in this syndrome. In 1 patient the clinical diagnosis was tumor of the brain. Bennett and Levine [36] recently described an instance of periarteritis nodosa involving cerebral and neural vessels, which clinically simulated chronic meningitis. Vance and Graham [37] reported a case of generalized lesions, including the vessels of the brain, in a young adult Negro for whom the diagnosis was established at laparotomy.

An analysis of our records shows that 8 patients had symptoms referable to the nervous system, 2 with peripheral neuritis. In 6 the

TABLE 4.—*Data on Neurologic Observations*

Case	Neurologic Symptoms	Postmortem Observations
1	Nuchal rigidity; positive Kernig sign	Intimal proliferation; occasional thrombosis; pigment-laden gitter cells; circumscribed areas of mucinous degeneration; productive meningitis; diffuse gliosis of brain
4	Convulsions; transient amaurosis	Not examined
5	Nuchal rigidity; convulsions; transient amaurosis; "encephalitis"	Not examined
7	Nuchal rigidity; positive Kernig and Brudzinski signs	Edema of brain; diffuse gliosis; perivascular gitter cells; thickened vessels
11	Left ankle clonus; numbness of left hand; convulsions; nuchal rigidity; myoclonus; spontaneous hippus movement of pupils	Not examined
12	Peripheral weakness of left side of face; nerve deafness on right; similar involvement of nerves on left; Ramsay-Hunt syndrome	Brain grossly normal except for enlargement of ventricles
16	Glovelike hyperesthesia—peripheral neuritis	Not examined
17	Bilateral ulnar neuritis; clouding of sensorium; polyneuritis; impairment of joint sense	Cortex of brain covered with gelatinous, edematous exudate underneath pia arachnoid; blood vessels moderately congested; perivascular infiltration with glia cells and fibrosis; occasional pigment-laden gitter cells in perivascular space; hyaline changes in vessels

symptoms were interpreted as due to encephalomeningitis, and necropsy showed a productive perivascular and meningeal reaction. In this connection it is interesting to recall Chvostek and Weichselbaum's patient who showed pupillary changes, rigidity of the neck and symptoms of encephalitis, which had been attributed to syphilis of the central nervous system.

In a recent case, the first reported in Belgium,[38] the patient presented the clinical signs of meningitis, in addition to articular pains, and hemor-

36. Bennett, G. A., and Levine, S. A.: Two Cases of Periarteritis Nodosa, Am. J. M. Sc. **177**:853, 1929.

37. Vance, B. M., and Graham, J. E.: Periarteritis Nodosa Complicated by Fatal Intrapericardial Hemorrhage, Arch. Path. **12**:521 (Oct.) 1931.

38. Van Bogaert, L.; Stolz, B., and Ley, R. A.: Sur une observation de périartérite noueuse a localisation neuro-cutanée, Ann. de méd. **31**:530, 1932.

rhagic spinal fluid was obtained on several occasions. Improvement occurred, but in six months all the symptoms recurred and bloody spinal fluid was obtained, with the additional finding of hemorrhagic nodules grouped and distributed like the lesions of herpes zoster. Again a remission occurred, followed by a terminal recurrence in which there were diplopia, strabismus, automatic movements, massive lumbosacral purpura, gangrene of one great toe and xanthochromic spinal fluid. The diagnosis was established by means of biopsy of the skin.

Though major vascular accidents involving the central nervous system have been infrequent thus far in this disease, they may be anticipated, and it is likely that in some cases idiopathic subarachnoid hemorrhage is on this basis.

TABLE 5.—*Lesions of Skin and Oral Mucous Membranes*

Case	
1	Purpura; erythematous maculopapules distributed diffusely
4	Blisters on tongue; swelling of face
5	Purpura of hip
6	Maculopapules on upper extremities; pulsatile nodules on face
7	Purpura in antecubital fossa
8	Scarlet fever followed by urticaria
11	Purpuric spots on back and pectoral region
12	Red swellings on legs, 5 cm. in diameter
13	Ulcerations of tongue and bucal mucosa; hemorrhagic skin lesions; fawn-colored maculopapules on neck and trunk ("erythema multiforme associated with tuberculosis"); herpetiform lesions about mouth
14	Purpura
16	Postular and sanguineous rash over face (medicamentosa?); white-centered petechiae on conjunctivae, shoulders and arms; erythematous macules on face; edema of ankles and eyelids
17	Papular rash of face (medicamentosa ?); urticaria of left hypothenar eminence; petechial hemorrhages; swelling of face
Total	12 cases

CUTANEOUS LESIONS

About 15 per cent of the patients reported on had cutaneous lesions. In 36 patients with cutaneous involvement studied by Alkiewicz,[39] the following types of lesions were present (some in combination): macules in 16 cases, nodules in 15, nodes in 11, extravasated blood in 7 and necrosis in 5.

Several cases have been reported in which the lesions were apparently restricted to the skin and subcutaneous tissues. Alkiewicz reported the case of a patient who for about two years presented chronic sepsis, with recurrent crops of nodes on the skin ranging from the size of a pea to that of a plum. These were slightly tender, dull red and slightly scaly. The areas were distributed irregularly over the extremities and back and became necrotic. Healing was slow and resulted in atrophy of the skin. No physical findings other than fever and facial edema

39. Alkiewicz, J.: Multiple nekrotisierende Periarteriitis nodosa der Haut, Arch. f. Dermat. u. Syph. **168**:522 ,1933.

were noted. Streptococci (unmentioned type) were cultivated from the necrotic areas; the blood cultures were sterile.

Periarteritis nodosa limited to the skin has been noted following erysipelas.[11] The patient was a 64 year old housewife with erysipelas of the forearm which lasted for one week. In two months lentil-sized elevated nodules of the skin occurred at the site of the erysipelas. The forearm was enlarged, though pitting edema was not present. Slightly indurated macules and slight marmoration also were present. Biopsy of the skin at this time showed pericapillary (arterial) and venous infiltration and typical fragmentation of the media elastica of the arteries. Otherwise the patient has remained well.

Lindberg [40] reported 2 cases of the disease with a long duration in which subcutaneous nodules were present. The first patient, a young girl, had an infected wound of the foot complicated by articular pains and finally by the appearance of subcutaneous nodules. Both the development and the subsidence of the nodules and of the severe constitutional symptoms were rapid. Several attacks occurred, one after apparent influenza. Biopsy and serial histologic examination showed segmental involvement of the subcutaneous vessels.

The second instance occurred in a man of 50 with long-standing, inadequately treated syphilis. Subcutaneous nodules appeared on the extensor surfaces of the extremities. Biopsy showed aneurysmal dilatation of the small arteries.

Matthes described pulsating subcutaneous nodules. In the patient with the clinical course of recurrent meningitis, already referred to, the severity of the cutaneous lesions paralleled that of the general condition. Thus the purpuric spots on one foot cleared and were followed by hemorrhagic nodules which were like the lesions of herpes zoster in their configuration and distribution. In the fatal recurrence massive purpura of the lumbosacral region was present, together with gangrene of one great toe. In addition to intracutaneous hemorrhage, biopsy of the skin disclosed typical arteritis, a homologous type of phlebitis and of pericapillary infiltration and also foci of the same cell constituents in relation to the cutaneous glands.

In another recent case of periarteritis nodosa,[41] the second reported in France, the initial cutaneous lesion was a scarlatiniform rash on the abdomen, which became purpuric and progressed to vesicle formation with blood-tinged contents. Superficial necrosis with blackened crusts was distributed over the tips of the ears, about the nares, at the tip of the chin and on the midportion of the mouth.

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40. Lindberg, K.: Ueber eine subkutane Form der Periarteriitis nodosa mit langwierigen Verlauf, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:159, 1933.

41. Hutinel, J.; Coste, F., and Arnaudet, A.: Périartérite noueuse de Kussmaul, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:46 (Jan. 27) 1930.

Thirteen patients in our series (76 per cent) had cutaneous lesions varying from transitory urticaria to ulcerative lesions. Urticaria, which is generally considered a cutaneous manifestation of an allergic state, has been noted in a few instances (our case 8, Lamb's case 1 and Ophüls' case). Actually, the significance of urticaria in the pathologic physiology of the blood vessels in this disease is not known. Edema with slow pitting, occasionally involving the face, has been observed several times. The variety of lesions listed in the accompanying table is striking. The resemblance to the pleomorphic lesions of erythema multiforme is evident. Erythema nodosum was the diagnosis made in the cases reported on by Klotz and Ophüls, and it was considered applicable

TABLE 6.—*Ocular Findings*

Case	Ocular Findings	Renal Lesions	Miscellaneous
1	Retinal exudates; hemorrhages of retinal arteries	Glomerulonephritis	Hypertension
5	Perivasculitis; hemorrhages of retinal arteries	Numerous minute renal infarcts	Hypertension
6	Neuroretinitis; fibrinous exudate of retina	Large renal infarcts; perirenal hematoma	Gradual increase in blood pressure
7	Obliterated disk margins; reddened disks; thin arteries; full veins; many exudates; few hemorrhages	Malignant nephrosclerosis	Hypertension before admission to hospital
9	Edema of retina and disk; complete amaurosis; no pupillary reaction to light	Renal infarctions	Hypertension
12	Edema of lids; chemosis of conjunctivae; episcleritis; iritis; normal fundi	Periarteritis nodosa of kidneys; renal hemorrhage	Hypertension
14	Thin, irregular retinal vessels	Arteriosclerosis	Senility
15	Papillitis; linear hemorrhages of retinal arteries; thin, irregular retinal arteries; old retinal exudates	Malignant sclerosis	Hypertension
17	No ophthalmoscopic findings	Renal infarctions; necrotic arterioles; proliferation of glomerular nuclei	Hypertension; "atypical verrucous endocarditis"; choroidal periarteritis nodosa

in our case 12. The pathognomonic aneurysmal lesion occurred in only one instance (case 6). Particularly interesting was the occurrence of white-centered petechiae in case 16, a finding usually associated with bacterial emboli, though occasionally with atypical verrucous endocarditis (in which blood cultures are characteristically sterile). This finding has not been reported previously in connection with periarteritis nodosa. Attacks of scarlet fever and urticaria (case 8), of erysipelas and cutaneous nodules and of posttraumatic cellulitis (Gray [42]) preceding periarteritis nodosa seem significant.

Since the skin proper is preeminently a capillary bed and contains few arterioles, it is an excellent indicator for involvement of the capillary portion of the vascular tree in this syndrome.

42. Gray, cited by Rothstein and Welt.[16]

OCULAR INVOLVEMENT

The routine ophthalmoscopic examination disclosed definite signs in 6 cases. Periarteritis nodosa of the choroidal arteries was described for the first time by Goldstein and Wexler [43] (our case 17) with no ophthalmoscopic evidence. In our case 12 portions of the eye other than the fundi were involved. Even more extensive involvement—iridocyclitis, episcleritis, orbital cellulitis and arteritis of the choroidal vessels—was reported in a 10 year old child.[44] Isolated necrotizing, inflammatory lesions of the small choroidal arteries were noted by Helpern and Trubek [45] in a patient who had gonorrheal urethritis complicated by ophthalmia.

Typical nodular lesions in the short ciliary arteries have been described.[45a]

The only report of typical involvement of the retinal arteries was made by P. Müller in 1899; he described changes similar to those in the small vessels in the brain. However, no subsequent observer has reported such characteristic lesions of the retinal arteries.

Herrenschwand commented on the frequency of albuminuric retinitis in periarteritis nodosa. Histologic studies were made by Friedenwald and Rones [46] of albuminuric retinitis in a case of periarteritis nodosa with the ophthalmoscopic findings of edema of the retina and optic disk, with marked arteriosclerosis, hemorrhages and cotton-wool exudates. Histologically, the typical characteristics of albuminuric retinitis were present; the retinal vessels were sclerotic and lacked the lesions of periarteritis nodosa, which, however, involved the choroidal arteries.

These authors also described a case of healed syphilis and arteriolosclerosis with nodules of inflammatory tissue related to sclerotic and partially thrombosed arterioles in the choroid. They cited this case as a connecting link between the vascular lesions of arteriolosclerosis and those of periarteritis nodosa.

The retinal lesions in cases of periarteritis nodosa are such as have occurred in association with essential hypertension, malignant sclerosis,

43. Goldstein, I., and Wexler, D.: The Ocular Pathology of Periarteritis Nodosa, Arch. Ophth. **2**:288 (Sept.) 1929.

44. Krahulik, L.; Rosenthal, M., and Loughlin, E. H.: Periarteritis Nodosa in Childhood with Meningeal Involvement, Am. J. M. Sc. **190**:308 (Sept.) 1935.

45. Helpern, M., and Trubek, M.: Necrotizing Arteritis and Subacute Glomerulonephritis in Gonococcic Endocarditis, Arch. Path. **15**:35 (Jan.) 1933.

45a. King, E. F.: Ocular Involvement in Periarteritis Nodosa, Tr. Ophth. Soc. U. Kingdom **55**:246, 1935. King described a case in which the diagnosis of periarteritis nodosa was established by biopsy and in which papilledema with secondary atrophy developed in one eye and in the other eye recurrent iritis with secondary glaucoma which necessitated enucleation. Pathologic examination revealed intense subacute uveitis and retinal periarteritis.

46. Friedenwald, J. S., and Rones, B.: Ocular Lesions in Septicemia, Arch. Ophth. **5**:175 (Feb.) 1931.

glomerulonephritis and prolonged infections. In Gruber's series 14 patients showed changes in the fundi, all of which were associated with some renal lesion. All of our patients who came to necropsy showed renal involvement, about half of them having lesions of the fundi, as determined clinically.

Obviously, one may consider albuminuric retinitis as an expression of the renal disease as such or of the periarteritis nodosa. Since the renal lesions are intimately associated with periarteritis nodosa, the system disease, even though the renal arterioles may not show the typical lesions of periarteritis nodosa, the dilemma may be more apparent than real.

Both hypertension and narrowing of the retinal arterioles have been observed to develop during the clinical course of periarteritis nodosa. Retinal arteriolosclerosis seems to be one of the accompaniments of periarteritis nodosa.

POLYSEROSITIS

In 7 of the cases in which necropsy was performed polyserositis of varying extent was associated with periarteritis nodosa as illustrated in the following summary:

Case	
1	Fibrinous pericarditis
4	Chronic peritonitis and pleurisy
8	Pleural, perihepatic and perisplenic adhesions; as noted at laparotomy, fibrinous exudate and edematous periduodenal tissue
9	Vascularization and thickening of the pericardium
10	Granular deposits in the pleurae
14	Adhesions in the right pleura, fibrinous granules and adhesions of the parietal pericardium
16	Serosanguineous fibrinous pleurisy and hydrothorax on the right
17	Pericardial adhesions and bullous edema of the visceral pericardium; a similar type of pleural involvement; thickened capsules of the liver and kidneys; peritoneal effusion

Similarly, Lamb's [47] 2 patients and Ophüls' patient had polyserositis. In Lamb's first patient asthma, urticaria and purpura were noted, and at postmortem examination fibrinous pleurisy, pericarditis and perisplenitis, as well as valvular vegetations and glomerulonephritis in all stages, were present. The second patient, who was considered to have appendicitis and pharyngitis, showed nephritis and arthritis postoperatively, and at postmortem examination there were effusions in the pleura, pericardium and peritoneum, periarteritis nodosa of the heart and kidneys, infarctions of the pancreas and a normal appendix.

Ophüls' patient also had symptoms treated by appendectomy and in several months showed subconjunctival hemorrhage, grossly bloody stools, asthmatic breathing and anasarca. At postmortem examination, in addition to the characteristic histologic picture of periarteritis nodosa, there were grayish nodules in the pleura, pericardium and myocardium. The nature of the nodules is extremely interesting: they had no distinct

47. Lamb, A. R.: Periarteritis Nodosa: A Clinical Pathological Review of the Disease, Arch. Int. Med. **14**:481 (Oct.) 1914.

connection with the blood vessels; they were granulomatous and consisted of young vascular connective tissue, containing eosinophils, plasma cells and swollen endothelial cells. This type of reaction was noted also in relation to the veins, perivascular lymphatic vessels, bronchi, interstitial myocardium, lymph nodes and spleen. The first patient of Middleton and McCarter's [48] series presented symptoms suggesting partial intestinal obstruction, which were explained by the necropsy observation of fibrous adhesions about the gallbladder, cecum and pelvic portion of the small intestine, free peritoneal fluid and fibrinous exudate. In addition, pleural fluid, fibrous adhesions of the pericardium and pleura and even a patch of pericardial calcification were present. Their third patient also had polyserositis.

TABLE 7.—*Leukocyte Count*

Case	On Admission	Later	Polymorphonuclears, Percentage
1	17,000	36,000	90
2	28,000	.....	80
3	39,000	.....	96
4	20,000	.....	80
5	40,000	12,000	90
6	38,000	54,000	75
7	35,000	16,650	86, 81
8	14,000	25,000	79, 80
9	12,000	.....	94
11	14,000	.....	80
12	18,400	12,000	85
	with 38% monocytes		
13	19,000	.....	90
14	10,700	.....	90
15	9,500	.....	80
16	10,650	.....	
	with 18% eosinophils		
17	10,200	6,580	87

Incidentally, our case 17 illustrates the transition from the effusive to the adhesive type of serositis. It will be recalled that though signs of fluid were present clinically and roentgenographically, no actual fluid could be obtained on aspiration.

One may infer that polyserositis is a tissue reaction in response to the underlying exciting agent analogous to the vascular reaction.

HEMATOLOGIC FINDINGS, TEMPERATURE AND PULSE RATE

Though leukopenia is occasionally present, leukocytosis is far more usual, counts of 40,000, 56,000 and 66,000 having been encountered relatively frequently. Such high leukocytosis is otherwise rare, sometimes occurring in lobar pneumonia.

The predominant cell type is the polymorphonuclear leukocyte, to the extent of 96 per cent. Striking eosinophilia has occurred in a minority of instances, the count being 23 per cent in Lamb's first case,

48. Middleton, W. S., and McCarter, J. C.: Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. **190**:291 (Sept.) 1935.

79 per cent in Strong's [49] case and 18 per cent in our case 16. The eosinophilia may be transient, and it may disappear when some surgical complication occurs. In one instance (case 12) a monocyte count of 38 per cent was present, and a diagnosis of monocytic leukemia was made. The high leukocytosis is correlated only with a high percentage of polymorphonuclear cells.

An increase in the number of blood platelets occasionally occurs.

Secondary anemia of varying degree may be present. Because of hemosiderosis of the spleen, the anemia has been attributed to hemolysis (cited by Gruber).

The tourniquet test has been positive in some instances.

No changes in the coagulability of the blood and in the bleeding time have been recorded.

By far the greater number of our patients showed the septic type of temperature curve; in a few the temperature was subfebrile or normal.

The pulse has been rapid.

HEALING IN PERIARTERITIS NODOSA

A number of instances of healing and of prolonged remissions in the course of this malady are on record. Erlandsson's [50] patient died one year after the diagnosis had been established by biopsy and had no lesions at postmortem examination (death was due to metastases from a carcinoma of the uterus).

Lindberg's [40] first patient with periarteritis nodosa of the subcutaneous type was sick for four years, and at the time of the publication of the case report he had been entirely well for one year. The patient reported on by Carling and Braxton-Hicks [51] had apparently recovered. Benedict's patient [52] was alive one year after the diagnosis had been established by biopsy of a subcutaneous nodule. At the later date only two nodules remained. Von Haun's [53] patient with subcutaneous nodes and fever was discharged to continue army service. Schottstaedt [54] reported a remission in a patient with cutaneous periarteritis nodosa; in these patients there was no evidence of nephritis in the urine.

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49. Strong, G. F.: Periarteritis Nodosa, Canad. M. A. J. **19**:534, 1928.

50. Erlandsson, S.: Neurologische Krankheitsbilder bei Periarteriitis nodosa, Acta psychiat. et neurol. **6**:369, 1931.

51. Carling, E. R., and Hicks, J. A. B.: Periarteritis Nodosa, Accidently Recognized During Life, Lancet **1**:1001, 1923.

52. Benedict, H.: Ueber Periarteriitis nodosa, Ztschr. f. klin. Med. **64**:405, 1907.

53. Von Haun, F.: Pathologische-histologische und experimentelle Untersuchungen über Periarteriitis nodosa, Virchows Arch. f. path. Anat. **227**:90, 1920.

54. Schottstaedt, W.: Case of Periarteritis Nodosa with Remission of Symptoms, California & West. Med. **36**:186, 1932.

Nephrectomy was performed on a woman because of renal hemorrhage due to aneurysm; she was alive and apparently well several years after the operation (Powell and Pritchard).

The patient of our series who was reported on by Manges and Baehr [4] had pulsatile nodules on the face, but by the time of her second admission to the hospital they had disappeared. Biopsy of a mesenteric artery during laparotomy at the onset of the disease revealed a cellular inflammatory lesion of the vessel wall. Later in the course of the disease biopsy of a branch of the temporal artery revealed a healing but cellular lesion. At necropsy most of the lesions consisted of irregular scars or degenerated areas in the vessel walls, chiefly in the media.

One patient with periarteritis nodosa was alive twenty-five years after the diagnosis had been made (cited by Alkiewicz). Three or 4 more instances might be cited. Perhaps time will permit the condition in our cases 2 and 3 to be demonstrated as arrested periarteritis nodosa.

The prognosis, thus, is not absolutely fatal but depends, among other factors such as toxemia, on the extent of the vascular involvement and on the importance of the impaired organs.

THE ERYTHEMA GROUP WITH VISCERAL MANIFESTATIONS IN RELATION TO PERIARTERITIS NODOSA

Case 1, in which the condition was first considered as belonging to the erythema group of Osler, is noteworthy because the apparent error may serve as a clue to the solution of this heterogeneous syndrome. The pathologic substratum of Osler's disease, as summarized by Christian,[55] is a focal disturbance in the small blood vessels—capillary, precapillary and postcapillary—which causes dilatation, diapedesis and exudation either singly or in combination. Actually, pathologic material is inadequate. Thus, there is a report by MacCallum and Watson on one of Osler's patients who died in uremia and in whom subacute glomerulonephritis was observed. There is also a report by Trimble [56] of a case in which the appendix was hemorrhagic and gangrenous. Few other references have been found. It seems significant that the papers on the Osler erythema group have appeared only in English, suggesting that studies of this syndrome have been made from a different approach, perhaps from the standpoint of the clinician rather than of the pathologist.

On considering the erythema group with visceral crises, it is found that the condition is diagnosed fairly often clinically and inadequately

55. Christian, H.: Visceral Disturbances in Patients with Cutaneous Lesions of the Erythema Group, J. A. M. A. **69**:325 (Aug. 4) 1917.

56. Trimble, I. R.: Erythematous Group of Skin Diseases with Especial Reference to Abdominal Pain, J. A. M. A. **96**:2010 (June 13) 1931.

studied pathologically, whereas in periarteritis nodosa the reverse has been true in the past. Indeed, Osler's emphasis on the admittedly miscellaneous collection of patients with "visceral manifestations of the erythema group" and his prophetic statment in 1914 [57] in regard to the "anaphylactic" mechanism on either an infectious or metabolic basis, is strikingly similar to Gruber's conception of periarteritis nodosa, which, to repeat, is not that of a unitary disease but of a peculiar hyperergic expression of sensitized portions of the arterial wall of one or several organs in the course of some usually prolonged infection or septic disease.

The clinical resemblance between these two syndromes, with their varying manifestations, is remarkable when one rereads Osler's [58] case reports and tentatively applies the diagnosis of periarteritis nodosa to them. For example, Osler's twentieth patient, a boy of 15, had an attack of severe colic and was admitted to the hospital for suspected appendicitis. In a week a purpuric erythematous eruption appeared on the legs, with acute nephritis and melena. The patient recovered. In other cases (cases 21 and 29) the condition apparently followed an acute infection, such as otitis media. In case 26, that of a woman aged 24, there were erythema, urticaria and purpura, a chill, followed by consolidation of the lower portion of the left lung with delayed resolution, enlargement of the lymph nodes and thrombosis of the femoral vein. There was gradual recovery, with subsequent acute nephritis and death in uremia. Seven of Osler's original patients died in uremia. Clinically, the vascular involvement was certainly greater than the capillary lesions suggested by Christian as the cause of Osler's syndrome.

The characteristics of the erythema group are also descriptive of periarteritis nodosa: (1) polymorphous lesions of the skin, which may be acute, circumscribed edema, urticaria, purpura or ordinary exudative erythema; (2) polymorphous visceral lesions—local serous hemorrhagic exudate in the gastro-intestinal tract causing crises of pain and hemorrhages, acute nephritis and certain rare pulmonary and other lesions, and (3) infiltration of the synovial sheaths, periarticular tissue and joints.

In 3 of Christian's 10 patients with the erythema group, the condition was thought to have been due to food sensitivity; in 2 it followed a sore throat; in 1 it was associated with a positive Wassermann reaction, and in 1, in whom there were purpura, abdominal pain, hematuria, melena and recurrent arthritis and fever, it occurred in the course of diffuse miliary tuberculosis, and at postmortem examination the kidneys

57. Osler, W.: Purpura with Visceral Lesions, Brit. M. J. **1**:517, 1914.

58. Osler, W.: On the Visceral Manifestations of the Erythema Group of Skin Diseases, Am. J. M. Sc. **127**:1 (Jan.) 1904.

were slightly enlarged, with small hemorrhagic foci of intertubular and intratubular distribution but without nephritis.

The clinical similarity of the erythema group with a septic or infectious component to periarteritis nodosa is inescapable, despite the fact that a common pathologic lesion or factor has not been demonstrated.

Osler pointed out the clinical resemblance, probably amounting to identity, between the erythema group and the Schönlein-Henoch group. Pratt [59] was impressed with the similarity between the Schönlein-Henoch group and Franck's capillary toxicosis.

On considering Schönlein-Henoch's purpura, one finds a similar lack of well studied pathologic material and a resemblance of clinical manifestations. Hemorrhages into the serosa and mucosa of the intestine are common and are the cause of abdominal symptoms. Dilated, lengthened, distorted capillaries have been observed in vivo. The syndrome has been described in epidemic form suggesting an infection.[60] It is of interest that in Lamb's first case of periarteritis nodosa the original diagnosis was purpura rheumatica.

An allergic etiology, both on an infectious and on a metabolic basis, also has been suggested frequently for Schönlein-Henoch's disease, just as for the erythema group, on speculative clinical and experimental grounds. The typical phenomena of the abdominal form were compared by Glanzmann [61] with those produced anaphylactically in dogs. Descriptions of Schönlein-Henoch's disease show a resemblance to those of the clinical aspects of periarteritis nodosa, especially in regard to hemorrhagic perforation of the gastro-intestinal tract and nephritis.[62] Unfortunately, no detailed report of the condition of the blood vessels has been found.

It seems that capillary lesions with a tendency to spontaneous recovery are most characteristic of the erythema and purpura rheumatica group, though larger vessels also have been involved. In distinction, the patients with this condition who ultimately proved to have periarteritis nodosa showed progressive and irreversible vascular damage involving generally the just visible arterioles principally, though also capillaries and veins.

It is not intended to reduce the three syndromes to the same common denominator solely on the basis of their protean symptoms but to abstract

59. Pratt, J. H.: Purpura and Hemophilia, in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 5, chap. 3, p. 117.

60. Morawitz, P., and Denecke, G.: Blut und Blutkrankheiten, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1926, vol. 2, p. 262.

61. Glanzmann, E.: Beiträge zur Kenntnis der Purpura im Kindesalter, Jahrb. f. Kinderh. **83**:271 and 379, 1916.

62. Goldstein, E.: Schönlein-Henoch's Purpura, M. Clin. North America **12**:869 (Nov.) 1928.

from the instances of the erythema group those cases in which there were definite pathologic characteristics of the more accurately known periarteritis nodosa. The three syndromes—Osler's erythema group, purpura rheumatica abdominalis and periarteritis nodosa—have similar clinical manifestations, probably the same types of causative mechanisms, and certainly in some instances, as in our case 1, the same pathologic lesions.

TABLE 8.—*Bacteria Associated with Periarteritis Nodosa*

Author	Source	Organism
Bomhard and Oberndorfer	Renal and splenic vessel	Staph. aureus
Gruber's review		
Lamb, case 2	Peritoneal fluid	Staph. aureus
	Cardiac nodule	Varied organisms including streptococcus
Klotz, case 2	Heart blood	Streptococcus
	Subcutaneous nodule	Staph. aureus; diphtheroid
	Gallbladder and hepatic vessels and bile	Staphylococcus and streptococcus
Klotz, case 1	Gallbladder bile	Streptococcus mitis
Beitzke		Streptococcus
Jonas, one case	Kidney	Streptococcus
	Adrenal glands	Influenza bacillus
Lamb, case 1	Peritoneal fluid	Streptococcus
	Necrotic lymph node	Streptococcus
	Heart blood	Streptococcus
Beattie and Douglas	Kidney	Streptococcus
Gruber	Tonsillar abscess	Streptococcus
Ophüls	Pericardial fluid	Diplostreptococcus
	Blood culture	Streptococcus in flask
Sternberg	Pulmonary vessels	Diplostreptococcus
Helpern and Trubek	Pulmonary valve	Gonococcus
Herrman	Blood culture	Sterile
	Heart blood	Staphylococcus
	Spleen	Streptococcus (necropsy diagnosis: streptococcus septicemia)
Manges and Baehr	Tonsils	Str. haemolyticus
Van Bogaert, Stolz and Ley	Sputum	Bacillus Friedländeri
Alkiewicz	Skin ulcer	Streptococcus
	Blood culture	Sterile
Hutinel, Coste and Arnaudet	Pulmonary nodule (postmortem)	Staph. aureus
Moolten	Spinal fluid	Meningococcus

THE ETIOLOGIC FACTORS

The bacteriologic observations in our cases were few and varied and will therefore be considered in conjunction with those of previous observers, though there are limitations to a consideration of data obtained from numerous sources.

In no instance has the rôle of some filtrable virus been other than conjectural.

Only 6 of Gruber's collection of patients through 1925 showed positive bacteriologic evidence. Including subsequent cases, the organism most frequently isolated was the streptococcus and then the staphylococcus; in single instances, the influenza bacillus and the gonococcus, respectively, were obtained. In 1 patient, previously referred to [41]

(with persistent diarrhea and rash varying from the scarlatiniform to gangrene), a seropurulent vaginal discharge was present, from which streptococci were obtained; on postmortem examination the lungs and the liver each contained a small abscess with staphylococcic pus. The etiologic importance of these bacteria could not be evaluated. Several injection experiments in animals were inconclusive.

The rôle of the gonococcus in the evolution of the disease was clearly determined in one instance (in the case reported by Helpern and Trubek). The organism was recovered at autopsy from the pulmonary valve of the patient, who had shown a development from gonococcic urethritis to subacute gonococcic endocarditis and finally to the microscopic characteristics of necrotizing arteritis and glomerulonephritis. This is the clearest example of a relationship between periarteritis nodosa and an infectious state.

In one recent case of proved and treated meningococcic meningitis in a previously healthy girl of 10 years the condition was complicated by arthralgia, abdominal pain and melena, which suggested the diagnosis of periarteritis nodosa, which was confirmed.[63]

The relation of Str. haemolyticus to the development of periarteritis nodosa is more inferential, partly because this organism is associated with a variety of disease entities. It appears as the essential bacterial factor in the prodromal illnesses of periarteritis nodosa, for instance, in acute tonsillitis (3 of our cases, Lamb's second case, both of Klotz' cases and in some of Gruber's cases); in scarlet fever (in our cases 8 and 10), and in erysipelas preceding the development of periarteritis nodosa at the site of the lesion.[11]

In a study of 165 cases of streptococcus sepsis Sigmund[64] found that one fifth of the patients had mycotic aneurysms apparently due to purely degenerative lesions of the vessels; some of the lesions closely resembled those of periarteritis nodosa but lacked the gross aneurysms. Different stages of vascular reaction were observed in experimental animals and were attributed to the particular state of immunity.

The impression has been strengthening that the rheumatic state is related to the syndrome of periarteritis nodosa. It has been suggested by Oskar Klotz, on the basis of clinical correlation, that periarteritis nodosa may be a vascular reaction occurring in the course of rheumatic fever and rheumatoid infections. Such a correlation is present in our cases 1, 8, 10 and 15, in which fresh Aschoff bodies and verrucous endocarditis were present and typical acute periarteritis as well. These have been reported in an article entitled "Periarteritis Nodosa (Necrotizing

63. Moolten, Sylvan: Personal communication to the author.

64. Sigmund, H.: Gefässveränderungen bei chronische streptokokken Sepsis, Centralbl. f. allg. Path. u. path. Anat. **35**:276, 1924.

Arteritis) Associated with Rheumatic Heart Disease" by Friedberg and Gross.[65] Neale and Whitfield (cited by Middleton and McCarter [58]) reported a case of chorea in a child treated with salicylates in which a similar association of rheumatic lesions and periarteritis nodosa occurred.

Besides this group of cases in which there were unmistakable lesions both of rheumatic fever and of periarteritis nodosa, there are some considered to be instances of rheumatic fever in which the condition seems to be associated with the erythema group of cutaneous diseases. In some of these cases, reported by Schloss [66] under the title "Association of Rheumatic Fever and the Erythema Group of Skin Diseases," such varied and atypical symptoms were presented as to suggest the clinical course in some of our cases of periarteritis nodosa. The pathologic involvement in this group was incompletely studied.

Coburn [67] has reported another type in which critical abdominal symptoms occurred in association with acute rheumatic fever. In a child sudden death followed an abdominal crisis. In addition to Aschoff bodies and valvular lesions, hemorrhages from serous membranes, pulmonary alveoli, ovaries and along the colonic vessels were present (Coburn's case 1). In another case (Coburn's case 7) symptoms suggesting appendical abscess following grip were found on laparotomy, to be explained by necrosis of peritoneal fat and were followed by pancarditis, polyarthritis, pleurisy, hematuria and melena. The appendix contained slightly dilated subserous vessels and clotted blood attached to the serosal surface. In his case 8 hemorrhagic appendicitis was followed by migratory polyarthritis and rheumatic carditis.

Coburn emphasized the fact that the condition is characterized by hemorrhagic lesions, which do not, however, depend on a specific change in the blood vessels and are not the accepted rheumatic lesion, though they frequently accompany typical endocardial involvement. The clinical observation has been made that patients with rheumatic fever who have abdominal symptoms are most likely to have associated periarteritis nodosa.

For the purpose of demonstrating a relationship of rheumatic fever to periarteritis nodosa, it has seemed tenable to grade the syndromes as follows: (1) those with the typical symptoms of rheumatic fever, (2) those disseminated symptoms suggesting the erythema group clinically,

65. Friedberg, C. K., and Gross, L.: Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, Arch. Int. Med. **54**:170 (Aug.) 1934.

66. Schloss, O.: Association of Rheumatic Fever and the Erythema Group of Skin Diseases, Am. J. M. Sc. **140**:226, 1910.

67. Coburn, A.: Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

(3) those with symptoms based on hemorrhagic vascular lesions which are neither specifically rheumatic nor typical of periarteritis nodosa and (4) those with the typical lesions of both syndromes and a variegated clinical picture.

Syphilis is not intimately related to periarteritis nodosa. In one recent case, periarteritis nodosa occurred in a syphilitic patient who was inadequately treated but who showed a serologically negative reaction (Lindberg). However, Jacobsen [67a] recently reported 2 cases of periarteritis nodosa associated with clinical and serologic evidence of syphilis in which an autopsy was performed.

Vascular lesions, especially thrombosing arteritis, which occur in the more severe forms of some specific infections—pneumonia, influenza, epidemic meningitis and secondary syphilis—may be one predisposing factor in the development of periarteritis nodosa.[68]

The fact that an infection so frequently precedes the onset of periarteritis nodosa within the course of a few months suggests that an etiologic relationship exists between the two conditions.

As has already been mentioned, experimental attempts to reproduce the disease by means of inoculation and subinoculation of crushed nodules have been inconclusive. Metz in 1931 produced lesions of the periarteritic type but without aneurysms in rats which were first sensitized to streptococci and then given injections either of these organisms or of nonspecific serum. Gerber [69] produced vascular lesions, including necrosis of the walls, thrombosis and hemorrhage, in various viscera in kittens by means of repeated intravenous injections of bacterial toxins. Also, in some animals preliminary preparation with an intradermal as well as an intravenous injection seemed to favor development of systemic vascular lesions. This experimental work suggests the susceptibility of blood vessels to repeated exposure to bacterial products.

The allergic state in its most characteristic clinical form is exemplified in case 16. The first clinical indications occurred in this patient at the age of 35 and consisted of attacks of asthma. Positive results of cutaneous tests to flour, barley and feathers were obtained in the patient, who was a baker. The asthma continued to be a prominent symptom in addition to the diarrhea, peripheral neuritis and cutaneous lesions. At necropsy two years after the onset, numerous pulmonary infarctions

67a. Jacobsen, V. C.: Periarteritis Nodosa, with Report of Two Cases Associated with Clinical Syphilis, in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, The Waverly Press, Inc., 1936, p. 820.

68. Harbitz, F.: Unknown Forms of Arteritis with Special Reference to Their Relation to Syphilitic Arteritis and Periarteritis Nodosa, Am. J. M. Sc. **163**:250 (Feb.) 1922. Derick, C. L., and Hass, G. M.: Diffuse Arteritis of Syphilitic Origin, Am. J. Path. **11**:291 (March) 1935.

69. Gerber, cited by Baehr, Klemperer and Schifrin.[73]

due to small thrombosed vessels were present which might be held accountable for the asthma. May allergy on a nonbacterial basis be associated with the development of periarteritis nodosa?[69a]

There is evidence pointing to the conception that glomerulonephritis with its associated vascular involvement is dependent on a mechanism of sensitization to a preceding disease which generally is of bacterial origin. (To cite this evidence briefly,[69b] glomerulonephritis complicating scarlet fever or tonsillitis develops when the primary disease has apparently receded; clinical symptoms which are extremely suggestive of glomerulonephritis occur in the course of serum sickness and of urticarial attacks; glomerulonephritis has been noted to occur in one third of the cases of Libman's bacteria-free and healed stages of subacute bacterial endocarditis and in only 1 per cent of the cases during the bacteremic phase; glomerulonephritis occurs[70] occasionally in the course of protracted infections associated with the gonococcus, pneumococcus, meningococcus and influenza bacillus; glomerulonephritis is claimed to have been produced successfully in animals immunized against streptococci and not in those unimmunized. Richet[71] described symptoms of glomerulonephritis in the course of an allergic reaction to horse dander. Acute nephritis may occur in the Schönlein-Henoch syndrome, either as part of the attack or in the course of the patient's life.)

Glomerulonephritis is frequently enough associated with periarteritis nodosa. Lamb's first patient had glomerulonephritis in all stages. Indeed periarteritis nodosa has occasionally presented the clinical course of glomerulonephritis, as in Damblé's[72] case, that of a 7 year old girl and in our cases 1, 4 and 17. Damblé raised the obvious question of their etiologic relationship.

Clinically, in cases in which the final diagnosis is glomerulonephritis the condition often suggests Osler's erythema group, not because of the heterogeneity of symptoms but because of the other evidences of vascular injury. For example, a 36 year old man with previously known albuminuria had a severe attack of acute tonsillitis, followed in several weeks by arthritis, purpura, pitting edema of the lower extremities and

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69a. Since the submission of this paper an interesting report of 3 cases in which the classic allergic symptoms were correlated with periarteritis nodosa has appeared (Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, J. A. M. A. **107**:1555 [Nov. 7] 1936).

69b. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931, p. 355.

70. Baehr, G.: Glomerular Lesions of Subacute Bacterial Endocarditis, Am. J. M. Sc. **44**:327, 1912.

71. Richet, C., and Dublineau, J.: Le purpura rhumatoïde de nature anaphylactique, J. méd. franç. **19**:182 (May) 1930.

72. Damblé, K.: Beitrag zur Pathologie der Periarteriitis nodosa, Beitr. z. path. Anat. u. z. allg. Path. **85**:619, 1930.

definite evidence of glomerulonephritis—an association of symptoms which clinically suggested Osler's disease. Our first patient with periarteritis nodosa gave a similar history.

Glomerular lesions,[73] occasionally to the extent of true diffuse glomerulonephritis, have been noted in patients with vascular disease associated with lupus erythematosis and endocarditis which may be etiologically related to periarteritis nodosa.

In glomerulonephritis associated with periarteritis nodosa one may tentatively assume that there are two manifestations of vascular sensitization, which, if considered as being independent of each other, would be improbable. Until disproved, it is fair to assume with Gruber that glomerulonephritis is a local reaction to the causative sensitizing agent of periarteritis nodosa. Because of involvement of the capillaries and pericapillary inflammatory cells, a clinical expression different from that when the medium-sized vessels are injured is produced.

Keegan [74] reported a case in which one kidney was removed at laparotomy because of a gross appearance suggesting miliary tuberculosis. These lesions proved to be those of periarteritis nodosa. The patient died two months later of renal insufficiency, and the other kidney showed early signs of arteriosclerosis and chronic vascular nephritis, apparently "healed" periarteritis nodosa. The relation of arteritis to renal disease, especially when localized to the kidneys, as in Fishberg's [69b] case, is convincing and recalls Jäger's thesis that healed periarteritis nodosa may terminate in lesions closely resembling arteriosclerosis, particularly in relatively young persons.

In the so-called malignant phase of essential hypertension the etiologic and pathogenic factors are conjectural. It has been suggested that there is a congenital predisposition in the vessels, that this is an accelerated form of arteriosclerosis and that lead or syphilis may be concerned. The vascular changes in the kidney, besides the arteriolosclerosis, are necrosis, endarteritis, thrombosis and periarterial cellular infiltration of the renal arterioles. Fahr [75] stated that a sharp distinction cannot be drawn between the necrotizing arteriolitis of the kidneys in malignant sclerosis and the extrarenal lesions of periarteritis nodosa. Clinically, it seems that, as with glomerulonephritis, the occurrence of the two is fundamentally related.

Periarteritis nodosa, in the strict sense of the nomenclature, can apply only to the final degree of disruption of the walls of arterioles

73. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), Tr. A. Am. Physicians **50**:139, 1935.

74. Keegan, J. J.: Primary Vascular Nephritis or Renal Periarteritis Nodosa, Arch. Int. Med. **36**:189 (Aug.) 1925.

75. Fahr, cited by Gruber.[9]

which have been the seat of a necrotizing inflammatory process. In a wider and probably more accurate sense periarteritis nodosa is part of a profound systemic response to infections of diverse types or possibly even to metabolic factors. The striking perivascular lesions themselves indicate the susceptibility of the component tissues of the blood vessels. For the present it is the relation of periarteritis nodosa to other vascular diseases and the analysis of their etiologic factors which deserve further elaboration.

SUMMARY

Fifteen cases of periarteritis nodosa with postmortem studies are presented.

More than half the patients had prodromal illnesses—acute tonsillitis, acute sinusitis, scarlet fever or sensitization asthma. Four had had rheumatic fever.

The usual mode of onset was with abdominal pain, associated with articular, cardiac or renal symptoms.

All the patients showed cardiac involvement. Twelve had lesions of the coronary arteries of varying degree; 4 had Aschoff bodies. One clinically presented the characteristics of the indeterminate type of verrucous endocarditis. Periarteritis nodosa may be a superimposed vascular reaction in the course of rheumatic fever.

Periarteritis nodosa of the pulmonary arteries was present in 5 cases; in 6 there were pulmonary lesions not immediately dependent on arteritis. Pleural pain, asthma or typical bronchopneumonia may be the clinical manifestation. The roentgen findings suggested bronchopneumonia or small pleural effusions.

All the patients who came to necropsy showed renal involvement, principally renal infarctions and aneurysms, and acute periarteritis nodosa. Three had glomerulonephritis; 2 had malignant sclerosis. These lesions may indicate a reaction involving blood vessels of different sizes but otherwise equivalent to the usual lesion.

Seven patients had surgical complications involving the gastrointestinal tract. Periarteritis nodosa was the cause of hemorrhagic pancreatitis in 3 cases. Three patients had periarteritic involvement of the appendix. Isolated lesions of "necrotizing arteriolitis" resemble histologically periarteritis nodosa without the clinical course of the latter.

Hepatic and cholecystic lesions secondary to periarteritis nodosa were infrequent in our series. Five patients had arteritic lesions of the liver, 1 had periportal fibrosis and 2 had fatty degeneration. Instances of associated cirrhosis have been noted.

Eight patients had neurologic symptoms; in 6 there was a clinical impression of encephalomeningitis. The lesions were due to productive perivascular and meningeal reactions.

A variety of cutaneous lesions were present in 12 patients, such as erythematous maculopapules, purpura, urticaria, herpes, edema, pulsatile nodules and white-centered petechiae. It is suggested that the smaller branches of the circulation are involved similarly to the arterioles.

Retinal exudates, neuroretinitis and thinning of the retinal arteries were noted in association with a variety of renal lesions in the course of periarteritis nodosa but in themselves were not pathognomonic. One patient showed a characteristic nodule of the choroid on microscopic examination.

Twelve patients had polyserositis, which is interpreted as a reaction of the serous membranes to the cause of periarteritis nodosa.

A leukocyte count as high as 54,000 may occur. The predominant cell type is the polymorphonuclear leukocyte, though striking eosinophilia and an instance of monocytosis have been noted.

Healing and prolonged remissions were noted, especially in patients without nephritic manifestations.

Some patients with the erythema group on further progress have proved to have periarteritis nodosa. It is suggested that similar clinical manifestations and mechanisms and occasionally the same pathologic lesions are present in these syndromes.

One case has been recorded in which the development from gonococcic urethritis to subacute gonococcic endocarditis and finally to the microscopic characteristics of necrotizing arteritis and glomerulonephritis was observed. Periarteritis nodosa complicating meningococcic meningitis has recently been observed. The bacteria principally implicated in the prodromes of periarteritis nodosa are the hemolytic streptococci. One patient in our series showed typical manifestations of an allergic state about two years before periarteritis nodosa was evident, and clinically the two conditions merged.

CARDIAC OUTPUT IN POLYCYTHAEMIA VERA

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Determinations of the cardiac output have not often been made in cases of polycythaemia vera. Early workers, who used unreliable methods, reported no marked deviation from normal. In 1925 Liljestrand and Stenström [1] found that the cardiac output was 10 per cent below normal in one case; the patient had a low basal metabolic rate (85 per cent of normal). The concentration of hemoglobin was 135 per cent, and the erythrocytes numbered 6,800,000 per cubic millimeter of blood. There was no enlargement of the spleen. The blood volume apparently was not determined. Ernst [2] in 1930 reported a cardiac output 10 per cent above normal in a case in which there was a 10 to 15 per cent increase in the basal metabolic rate. A diagnosis of polycythaemia vera was not warranted in this case, as the total blood volume, instead of being increased, was low, only 70 cc. per kilogram of body weight. Relative polycythemia was present, as shown by the value for hemoglobin, by the erythrocyte count and by the percentage of cells as determined with the hematocrit. The spleen was not palpable. Grollman [3] stated that studies of the cardiac output in a few additional cases have shown a variation of ± 10 per cent from normal, but he gave no data. No further reports have been found in the recent literature.

In the following case of polycythaemia vera all the classic features of the disease were present: an increased number of erythrocytes, an elevated value for hemoglobin, a high percentage of cells as determined with the hematocrit, a markedly increased total volume of blood, a palpable spleen, the characteristic congestive appearance of the skin and a history of venous thrombosis. Studies were conducted at intervals over a period of eight months, during which time treatment with

* Now residing in New Orleans.

1. Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of the Heart During Rest: II. The Influence of Variations in the Haemoglobin Content on the Blood Flow, Acta med. Scandinav. **63**:130-131, 1925.

2. Ernst, Curt: Beitrag zur Frage des Kreislaufes bei der Polycythaemia vera, Ztschr. f. klin. Med. **114**:757-764, 1930.

3. Grollman, Arthur: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

phenylhydrazine was carried out. For determinations of cardiac output the acetylene method of Grollman [4] was used, each test being made under basal conditions.

REPORT OF CASES

CASE 1.—A married woman of Swedish descent, aged 53, came to the clinic on Aug. 7, 1933, complaining of weakness, loss of weight and purplish red face and hands. She had had influenza ten years before and had undergone appendectomy at the age of 23. She had five children, one of whom had diabetes; a sister was anemic and took liver. In 1929 she had first noticed that the hands and face became bluish on exposure to cold and became red and flushed in a warm atmosphere. The tongue and mouth had been purplish red. She had reached the menopause in 1930 and had had hot flashes for two years. Since 1930 tinnitus had been a constant symptom. In August 1932, after an attack of severe pain in the left upper portion of the abdomen, the spleen was found to be enlarged. About the same time thrombosis of one of the superficial veins of the left leg occurred. In the three years prior to her admission to the clinic the patient had lost 67 pounds (30.4 Kg.), and for nine months weakness had forced her to remain in bed. In the year prior to her admission to the clinic she had noticed frequent palpitation, dizziness and slight pain in the thorax. Anorexia, flatulence and chronic constipation had been prominent complaints.

On physical examination the patient was markedly emaciated. Her height was 5 feet and 3 inches (160 cm.), and she weighed 83 pounds (37.6 Kg.). The skin of the face, especially across the nose and cheeks, and the lips, tongue, tips of the fingers and nail beds were a pronounced reddish blue. The blood pressure was 100 systolic and 70 diastolic, and the pulse rate was 90 beats per minute. The lymph nodes in the neck, axillae and groin were palpable. The veins of the legs showed marked varicosities, and those of the abdomen were dilated. The fingers were slightly clubbed. The heart and lungs were apparently normal. The spleen was markedly enlarged, extending below the umbilicus. A small umbilical hernia was present. Ophthalmoscopic examination revealed marked venous dilatation and a cyanotic appearance of the fundi. A diagnosis of polycythaemia vera was made as a result of the foregoing findings and the laboratory studies.

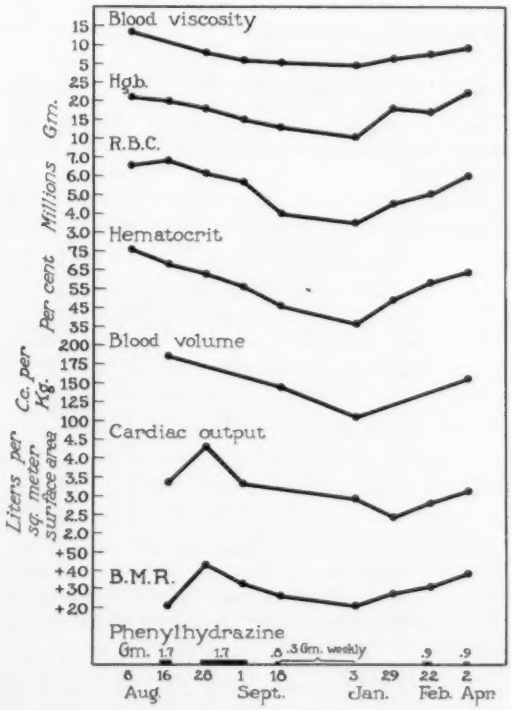
The patient was hospitalized, and treatment with phenylhydrazine was instituted. By August 18 1.7 Gm. of phenylhydrazine hydrochloride had been administered, and the urine showed evidence of considerable destruction of blood. At this time splenic infarction and diaphragmatic pleurisy developed; so medication was temporarily discontinued. On August 24 acute thrombophlebitis of the varicosities of the right leg developed, accompanied with moderate pain. Medication was resumed on August 26, another 1.7 Gm. of phenylhydrazine being given by September 3. No other untoward symptoms appeared during the patient's stay in the hospital, and she was dismissed on September 27 on a maintenance dose of 0.3 Gm. of phenylhydrazine hydrochloride once a week. By this time she had gained 7 pounds (3.2 Kg.) and was feeling much improved, and the hematologic findings were normal.

The patient returned on Jan. 2, 1934, for examination, occasional tinnitus and palpitation being her only complaints. She had gained 30 pounds (13.6 Kg.). Discoloration of the skin and mucous membrane was much less marked. The

4. Grollman, Arthur: Solubility of Gases in Blood and Blood Fluids, J. Biol. Chem. **82**:317-325 (May) 1929.

heart was slightly enlarged, and a systolic murmur was audible over the entire precordium. The spleen and liver were enlarged. After a number of laboratory tests were made the patient was dismissed on January 4. The same day she fell on the ice, fracturing the neck of the left femur. During her long stay in the hospital as a result of this mishap, further investigations were carried out.

The laboratory findings during the time the patient was under observation are given in the accompanying figure. At the time of her first admission to the hospital she had a high total blood volume, 185 cc. per kilogram of body weight, with a plasma volume of 59 cc. per kilogram. The viscosity of the blood was



The cardiac output and the hematologic values in polycythaemia vera (case 1).

increased to 13.6; the value for hemoglobin was 21.3 Gm. per hundred cubic centimeters, and the erythrocytes numbered 6,700,000 per cubic millimeter. The hematocrit reading was 73 for the percentage of cells. All these abnormally high values were reduced under treatment and remained nearly normal or slightly subnormal until March (no phenylhydrazine had been given for one month), when they began to rise rapidly. The leukocyte count was persistently elevated, and it increased during the intensive administration of phenylhydrazine. The differential count revealed neutrophilia and the presence of an occasional myelocyte. The values for blood urea, uric acid, sugar, calcium, phosphorus,

chlorides and serum proteins were normal. The albumin-globulin ratio was 1.7 : 1. The urine consistently contained albumin and erythrocytes. The number of blood platelets and the coagulation and bleeding time were normal. An electrocardiogram disclosed left ventricular preponderance, with an inverted T wave in lead III and some nodal premature contractions. The basal metabolic rate was elevated, a finding not uncommon in cases of polycythaemia vera, the cause of which is unknown. Table 1 gives the detailed findings throughout the period of observation on the cardiac output and basal metabolism, whereas the figure shows the relationship of these factors to the condition of the blood. According to Grollman, the cardiac output of a normal subject under strictly basal conditions is remarkably constant and is proportional to the area of body surface. Under strictly basal conditions a normal adult has a cardiac output of 2.2 ± 0.3 liters per minute per square meter of body surface.

The cardiac output of this patient at the beginning of treatment was considerably above normal, 3.37 liters per minute per square meter of body surface, and on one occasion it rose to 4.3 liters (table 1). At this time the basal metabolic rate was +43 per cent. On September 1 the cardiac output per square

TABLE 1.—*Cardiac Output in a Case of Polycythaemia Vera (Case 1)*

Date	Surface Area, Sq. Meters	Blood Pressure	Pulse Rate	Oxygen Consumption, Cc. per Sq. Meter per Minute	Basal Metabolic Rate	Cardiac Output, Liters per Minute per Sq. Meter of Surface Area	Systolic Output, Cc.
8/16/33	1.32	100/62	88	148	+21	3.55 3.20	53 48.5
8/28/33	1.33	120/64	80	174	+43	4.30	65
9/ 1/33	1.34	108/70	90	160	+33	3.30	49
1/ 3/34	1.47	100/64	70	149	+21	2.9	61
1/29/34	1.47	114/74	80	154	+27	2.4	43
2/22/34	1.47	106/72	87	154	+31	2.8	47
4/ 2/34	1.48	114/88	94	165	+38	3.1	48

meter was 3.3 liters per minute, and the basal metabolic rate was +33 per cent. The viscosity of the blood and the value for hemoglobin were practically normal, and the erythrocyte count and the percentage of cells as determined with the hematocrit were only slightly elevated (figure). The volume of blood on September 18 was somewhat reduced but was still considerably above normal. When the patient returned on Jan. 2, 1934, the volume of blood had dropped almost to normal; other findings revealed slight anemia. The basal metabolic rate was still elevated, +21 per cent, but the cardiac output was now 2.9, which, while not normal, showed an approach toward that figure. On January 29 the cardiac output was 2.4 liters per minute per square meter, within the normal range, and the basal metabolic rate was +27 per cent; on February 22 the output was 2.8 liters and the basal metabolic rate +31 per cent. On April 2 the cardiac output had risen to 3.1 liters and the basal metabolic rate to +38 per cent. The volume of the blood, number of erythrocytes, the value for hemoglobin and the percentage of cells as determined with the hematocrit also had increased at this time.

While the elevation of the metabolic rate in this case may partially account for the increased cardiac output, it could not have been the

entire cause. Perusal of the foregoing data shows that in the individual determinations the cardiac output did not always vary directly with the basal metabolic rate, although both curves follow the same general trend. The cardiac output was increased more than the oxygen consumption at the beginning of treatment, as the arteriovenous oxygen difference was below normal. The increased cardiac output cannot therefore be attributed only to the increased tissue metabolism. Similar findings were cited by Grollman in cases of hypertension in which there was an elevated basal metabolic rate and also in cases of hyperthyroidism by Boothby and Rynearson.[5] The last-named investigators showed that the cardiac output of patients with exophthalmic goiter was increased above the values produced in normal subjects by work that caused a similar increase in the consumption of oxygen. In the present case the cardiac output was increased above the normal curve produced by work to about the same extent as in cases of hyperthyroidism.

One can only theorize in regard to the cause of the additional elevation of the cardiac output in this case of polycythaemia vera. Considering only the factor of the increased concentration of hemoglobin in the blood, a decreased cardiac output might be expected. In cases of anemia in which the concentration of hemoglobin fell below 50 per cent, Dautrebande found an increased cardiac output. In studying the cardiac output at high altitudes Grollman found an initial increase when the subject ascended to a high level, with a gradual reduction in the cardiac output as the amount of hemoglobin in the blood increased. In polycythemia an increased percentage of hemoglobin is associated with a markedly increased total volume of blood, an increased number of erythrocytes per unit of blood, an increased viscosity of the blood and consequently a decreased amount of serum. Any of these three factors might influence the volume of the blood put out by the heart per minute. Ingestion of fluid has been found to cause a rise in the cardiac output, which conceivably is due to the sudden dilution of the blood, with a decreased carrying capacity for both oxygen and carbon dioxide of a unit volume of blood, or to an increase in the blood volume. Locke's solution increases the output more than does the ingestion of water, probably from the latter cause. Gregg and Wiggers [6] have stated that the expected hemodynamic effects in polycythemic hypervolemia would be similar to those produced through an increased venous return plus greater viscosity of the blood, namely, a rise in the venous pressure,

5. Boothby, W. M., and Rynearson, E. H.: Increase in Circulation Rate Produced by Exophthalmic Goiter, Compared with That Produced in Normal Subjects by Work, Arch. Int. Med. **55**:547-557 (April) 1935.

6. Gregg, D. E., and Wiggers, C. J.: The Circulatory Effects of Acute Experimental Hypervolemia, Am. J. Physiol. **104**:423-432 (May) 1933.

an increase in the diastolic size of the ventricles and an augmented systolic discharge with a rise in the arterial pressure. In acute experimental hypervolemia in dogs they found an increased return of blood to the heart, with an increased systolic discharge from the left ventricle.

The increase in the number of erythrocytes in polycythemia is necessarily associated with a decrease in the plasma volume per unit of blood. Most of the nutrients to the tissue, aside from oxygen, are carried in the plasma. If insufficient plasma is present to act as a solvent for these substances from the gastro-intestinal tract, it is possible that an increased demand by the tissues for more nutrient material could be a factor in bringing about an increased cardiac output.

In this case of polycythemia when the blood volume and hematocrit readings were elevated the cardiac output was increased. When these values had returned practically to normal the cardiac output was lowered and the arteriovenous oxygen difference was more nearly normal, the cardiac output tending, on the average, to vary with the amount of oxygen consumed. As the blood volume and hematocrit readings rose again, the cardiac output became elevated. It is possible that the increased volume of blood could influence the output of the heart and also that the increased viscosity could play a part. Another factor could be the increased demand of the tissue for nutrients, due to a decreased amount of serum per unit of blood, thus causing an increased output per minute. There is another question which is important in the determination of the cardiac output by a gas method in cases of polycythemia, and that is the difference in solubility of acetylene in polycythemic and in normal blood. Grollman found a slight difference in the solubility of this gas in the blood serum and in the corpuscles of the dog. In one case of polycythemia the solubility of acetylene was 0.71 cc. of the gas in 1 cc. of blood, as compared with 0.74 cc. of the gas in 1 cc. of normal blood; this difference, however, does not seem great enough to affect measurably the calculated cardiac output.

Cases 2, 3 and 4.—Determinations of the cardiac output and detailed studies of the blood have been carried out in three other cases of polycythaemia vera (table 2). In case 2 there was a normal cardiac output, and the basal metabolic rate was within normal limits. The volume of blood, the viscosity and other values were considerably elevated. In case 3 the cardiac output was essentially within normal limits, although there was a definite drop in the output as the volume of blood, the viscosity and the hematocrit reading returned toward normal. At the time of the third determination this patient had anemia, which might have accounted for the fact that the cardiac output was again increased. In case 4 there was a slight elevation of the cardiac output, with a normal basal metabolic rate, the cardiac output dropping as the blood volume, the hematocrit reading, the hemoglobin content and the erythrocyte count returned to normal.

None of these three patients showed a marked deviation from the normal in the cardiac output. In cases 3 and 4, however, there was a suggestion of correlation between the cardiac output and the hematologic status, all the values decreasing at the same time. The largest volume of blood and also the largest cardiac output were noted in case 4. None of these patients exhibited the marked elevation of blood volume which was present in case 1. It may be that the volume of blood must be greatly elevated to augment the cardiac output. Further determinations correlating the changes in the blood and in the cardiac output are necessary to warrant a definite conclusion.

TABLE 2.—*Cardiac Output, Metabolic Rate and Hematologic Values in Polycythaemia Vera*

Case	Date	Cardiac Output, Liters per Minute per Sq. Meter of Surface Area	Basal Metabolic Rate	Blood Volume Cc. of Whole Blood per Kg. of Body Weight	Blood Viscosity	Hematocrit Reading, Percentage	Hemoglobin, Percentage	Erythrocytes, Millions
2	.....	2.18	−2	137.0	13.0	73.0	20.9	6.50
3	5/18/34	2.49	+9	131.0	11.6	69.5	21.2	8.45
	5/29/34	2.02	+5	88.4	5.6	37.7	12.3	4.96
	6/ 4/34	2.60	+1	.....	....	30.0	10.6	2.69
4	5/29/35	3.00	+7	188.0	10.0	67.8	22.3	6.47
	6/ 6/35	2.80	+6					
	6/30/35	2.46	−2	95.0	....	46.0	14.8	4.73

SUMMARY

Determinations of the cardiac output and detailed studies of the blood have been carried out over a period of eight months in a case of polycythaemia vera. The cardiac output, which was elevated considerably above normal prior to the institution of treatment, decreased as certain hematologic values approached normal. The increase in the basal metabolic rate in this case does not entirely explain the increased cardiac output. It is suggested that the increased volume of blood may be a factor in this regard. Another factor may be the decreased percentage of plasma per unit of blood, causing a deficiency in the transportation of nutrient substances to the tissue. The cardiac output in three additional cases of polycythaemia vera is reported; in two the findings were within normal limits, and in one there was a slight elevation of the output. Two of these patients were followed during treatment, and it was observed that the cardiac output tended to decrease as the blood picture approached normal.

MONOCYTIC LEUKEMIA

REPORT OF EIGHT CASES

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In 1913 Reschad and Schilling-Torgau [1] reported the first case of monocytic leukemia. Two years later the second case was described by Fleischmann.[2] In 1930 Dameshek [3] reviewed the literature and found only ten acceptable case reports. Clough [4] in 1932 brought the number up to twenty-three.

On a subsequent examination of the literature a total of seventy-seven reports of well established cases were found. Of these four had not been available to previous reviewers, and seventy-three have appeared since Clough's report. The addition of eight cases which have come under our observation and which are herein presented brings the total number of acceptable cases described to eighty-five. In addition to these, approximately twenty-five case reports have been rejected because of insufficient or unconvincing data.

Monocytic leukemia has always been regarded as an exceedingly rare disease. However, the many case reports which have been published since interest in the condition has been aroused and the appearance of eight cases in New Haven in a period of three years suggest that it is considerably more prevalent than was previously supposed. From January 1933 to January 1936 forty-eight cases of leukemia were recorded in the New Haven and Grace hospitals and were distributed as follows:

	Myelogenous	Lymphatic	Monocytic	Unclassified
Acute	6 (13%)	9 (19%)	8 (17%)	1
Chronic	12 (25%)	12 (25%)		

From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service of the New Haven Hospital and Grace Hospital.

1. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeite dieser Zellen, München. med. Wchnschr. **60**:1981 (Sept. 9) 1913.

2. Fleischmann, P.: Der zweite Fall von Monozytenleukämie, Folia haemat. **20**:19 (Oct. 1) 1915.

3. Dameshek, W.: Acute Monocytic (Histiocytic) Leukemia, Arch. Int. Med. **46**:718 (Oct.) 1930.

4. Clough, P. W.: Monocytic Leukemia, Bull. Johns Hopkins Hosp. **51**:148 (Sept.) 1932.

Levine [5] reported that of six thousand and sixty-six autopsies performed at the Cook County and Grant hospitals, of Chicago, between 1931 and 1934, there were fifty-eight in cases of leukemia, of which thirty-six were cases of acute leukemia. Six of these were cases of monocytic leukemia which constituted 10.3 per cent of all the cases of leukemia and 16.7 per cent of the cases of acute leukemia. Doan and Wiseman [6] reported that of seventy-six cases of leukemia studied from 1930 to 1934, 12 (or 16 per cent) were instances of the monocytic type. If the incidence of monocytic leukemia ranges between 10 and 17 per cent of all cases of leukemia, as these figures suggest, it is evident that in general many cases are being overlooked.

REPORT OF CASES

CASE 1.—J. J., a 65 year old married, unemployed Negro (formerly a coal heaver), entered the New Haven Hospital because of sore throat and bleeding gums of four weeks' duration. As a child he had whooping cough and measles. Gonorrhea developed when he was 18. When he was a young man he is said to have had syphilis and to have received injection treatments until the Wassermann reaction became negative. Eight years before his admission to the hospital he suffered from attacks of asthma, which responded to treatment. Ten months before his admission to the hospital he was treated for a chronic ulcer of the anterior surface of the right leg, which healed after treatment with local applications. At that time it was recorded that his diet was inadequate in foods containing protein and vitamins. There was no lymphadenopathy and the liver and spleen were not enlarged.

Four weeks before his admission to the hospital increasing soreness of the throat, mouth, tongue and gums began, with slight intermittent bleeding from these mucous membranes. Two weeks later enlargement of the cervical lymph nodes and swelling of the ankles were noted. There had been a loss of 10 pounds (5 Kg.). Dietary deficiency was evident. His family of four adults had been subsisting on $4 a week.

Physical Examination.—The patient was undernourished, pale, weak and obviously seriously ill. Dyspnea on slight exertion was evident. There were numerous isolated purpuric spots on the skin. The gums were boggy and bled easily. The tonsils were enlarged; they were a peculiar gray and bore small patches of greenish gray exudate. There were hemorrhagic spots on the mucous membranes of the mouth and tonsils. Sclerotic changes of the vessels of the fundus oculi were present, and hemorrhagic spots and a few small scars were seen. The lymph nodes of the cervical, occipital, axillary, inguinal and epitrochlear regions were moderately enlarged but not tender. The heart was slightly hypertrophied, and a systolic murmur was heard over the entire precordium. There was pronounced sclerosis of the arteries accessible to palpation. Abdominal and neurologic examinations revealed no abnormality.

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5. Levine, V.: Monocytic Leukemia, Folia haemat. **52**:305 (Sept.) 1934.

6. Doan, C. A., and Wiseman, B. K.: The Monocyte, Monocytosis and Monocytic Leukosis: A Clinical and Pathological Study, Ann. Int. Med. **8**:383 (Oct.) 1934.

Laboratory Examination.—The patient's blood was in group 1, according to the classification of Jansky. The Kahn test for syphilis was negative. Blood cultures were sterile. There were 150,000 platelets per cubic millimeter of blood, according to the method of Rees and Ecker. The bleeding time was eight minutes. The clotting time was two minutes and forty-five seconds by the capillary method and three minutes and thirty seconds by the test tube method. The number of erythrocytes decreased from 2,100,000 per cubic millimeter at the time of the patient's admission to the hospital to 1,500,000 before his death, and the hemoglobin value declined from 40 per cent (6.1 Gm.) to 30 per cent (4.6 Gm.). The leukocyte count, on the other hand, increased rapidly from 61,000 to 179,000 per cubic millimeter. The cells of the monocytic series constituted from 89 to 96 per cent of the leukocytes. Ninety-five per cent of the leukocytes contained oxidase. The erythrocytes were hypochromic, an occasional normoblast was seen and moderate anisocytosis and poikilocytosis were noted. No sickle cells were seen.

The predominating leukocytes varied markedly in size; some were unusually large, but the majority ranged between 10 and 15 microns in diameter. The nuclei were round, oval or indented, the adult horseshoe shape being practically absent; in a number of instances the nuclei were grossly irregular or lobed. The diffuse homogeneous network of chromatin was typical of the monocyte, and its color varied with the intensity of the stain from grayish blue to purple. Occasional nucleoli were seen. The nuclear outline was unusually indistinct. The cytoplasm was scant in most cells and abundant in a few. It had a hazy, pale blue, ground glass appearance, with vacuoles in some of the cells. The majority of the cells contained no visible granules; in only a few were small lilac granules seen. The outline of the cells was usually irregular, scalloped or interrupted by budlike projections or actual pseudopodia. No clasmatocytes (Sabin) were seen.

Supravital studies showed that the predominant leukocytes were from 10 to 15 microns in diameter and were ordinarily motile. This activity consisted of a slow change in form, with actual progression seen in some instances. The nuclei were more often horseshoe shaped, bean shaped and irregular than was apparent in fixed smears. Practically all the leukocytes contained salmon-red, neutral red vacuoles grouped in clusters, which in the less actively motile cells assumed the characteristic rosette arrangement. Peripheral to the neutral red vacuoles, mitochondria in varying numbers were scattered throughout the cytoplasm.

The phagocytic activity of the leukocytes was studied with trypan blue. When this dye was added to the blood in vitro, 75 per cent of the leukocytes took it up. Thirty cubic centimeters of a 5 per cent solution of the dye was injected intravenously. Samples of blood drawn after five, ten and twenty minutes were studied, and it was found that in the first sample a few cells contained trypan blue granules, whereas in subsequent samples there were granules in 50 and 94 per cent of the leukocytes, respectively.

The urine was normal except for occasional hyaline and granular casts. The feces contained varying amounts of occult blood, detected by the guaiac test, and mucus in small amounts. Roentgenographic examination of the wrists, hands, tibias and fibulas were negative. Biopsy of an inguinal lymph node was performed, and a description will be given subsequently.

Clinical Course.—The temperature varied between 99.4 and 103.5 F., with daily swings to both extremes. The patient rapidly grew worse, and ulceration of the tonsils and gums increased progressively. No specific therapy other than small

doses of potassium arsenite was attempted. Death occurred twelve days after the patient's admission to the hospital. The total duration of the disease was approximately forty days.

Necropsy.—The anterior cervical, posterior cervical, submental, submaxillary, supraclavicular, axillary, inguinal and mesenteric lymph nodes were enlarged, the largest measuring 2.5 cm. in length. The hilar and mediastinal lymph nodes were not hypertrophied. On microscopic examination the normal architecture of an inguinal lymph node removed during life was seen to have been entirely replaced by large mononuclear cells resembling those seen in germinal centers. They contained large, round or oval, vesicular nuclei which varied considerably in size, shape and staining intensity. They had scanty rims of pink-staining cytoplasm, and these cells were frequently seen in a state of mitotic division. The capsule and adipose tissue at the hilus were invaded by these cells.

No thymic tissue was recognized.

The spleen weighed 495 Gm. The splenic pulp bulged slightly from the capsule on the cut surface, but it was dry and red-brown. The malpighian bodies could not be distinguished. Microscopically the picture was similar to that of the lymph nodes. The follicles could barely be recognized. Staining indicated an increased amount of reticulum.

The liver weighed 2,350 Gm. On section the lobular markings were distinct, and the red-brown surface was spotted with minute gray dots, concentrated in the periportal regions. Microscopically, the hepatic sinusoids were dilated, and the hepatic cords were atrophied. In many places, particularly in the periportal spaces, the compression of tissue by the mononuclear cells was so marked that large islands of these cells were formed. Most of the cells were round and had large, round, pale nuclei and little cytoplasm. Some were foamy and had large amounts of cytoplasm and small nuclei. Others were small and had small hyperchromatic nuclei, which were round, irregular or lobulated. These cells did not resemble polymorphonuclear leukocytes. In places groups of basophilic cells were seen. In the sinusoids Kupffer cells appeared in various stages of morphologic change. Occasionally some rounded ones were seen lying free in the lumens. Others were partially attached to the walls of the sinusoids.

The bone marrow of the sternum and vertebral bodies was red and cellular. The normal marrow was replaced by the typical mononuclear cells. Many of these appeared to be attached to the reticular network. The absence of granulocytes was evident with both Wright and Giemsa stains. A photomicrograph of the bone marrow from a vertebra is presented in figure 1 *A*.

There was extensive infiltration of the heart, aorta, lungs, stomach, intestines, pancreas, adrenal glands, kidneys, prostate, testes, tonsils, thyroid gland and skin with typical mononuclear cells. There were scattered petechial hemorrhages in varying degree into these organs.

CASE 2.—C. B., a 23 year old dentist's assistant, white, American, unmarried, entered the New Haven Hospital complaining of weakness and metrorrhagia. Except for chickenpox, measles, mumps, a tonsillectomy at 7 years of age and an appendectomy at 11 years, the patient's general health had been good until the present illness. Five and a half months before her admission to the hospital a generalized rash of purpuric spots developed. Subsequently similar spots appeared in smaller numbers. With the onset of purpura the patient first noted headache in the occipital region, backache and urinary frequency, which was ascribed by her physician to pus in the urine. At the same time leukocytosis was discovered. Despite the administration of solution of potassium arsenite, the weakness and

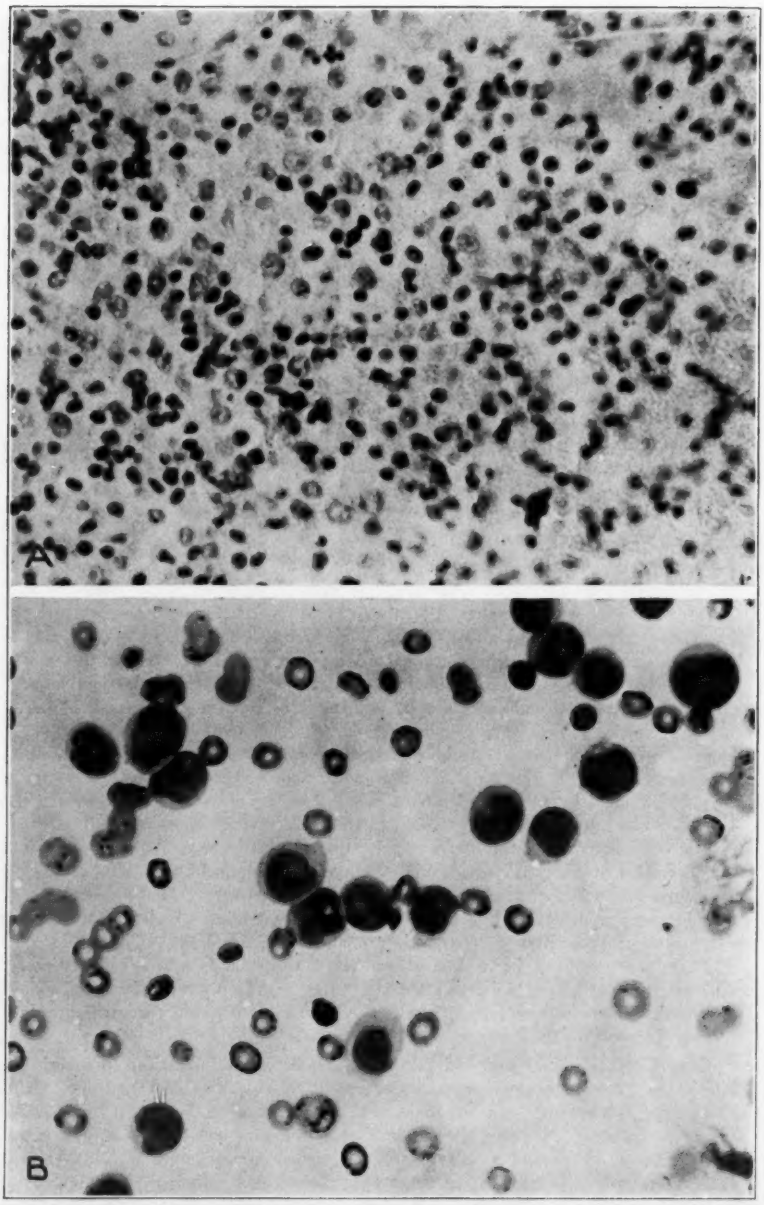

Fig. 1.—*A* (case 1), photomicrograph of bone marrow from a vertebra; × 500. The normal cells of the marrow have been replaced by a dense infiltration of typical mononuclear cells. Normoblasts and other young cells of the erythrocytic series are visible, but cells of the myelogenous series are rarely seen. *B* (case 2), photomicrograph of the blood; × 500. These leukocytes belong to the monocytic series. Note the variation in the size of the cells and the shapes of the nuclei. Evidences of pseudopodial activity are present, and in some of the cells nucleoli are visible. The dark shadows in the erythrocytes are a staining artefact.

palpitation became steadily worse. Menorrhagia with the passage of clots commenced two weeks before and persisted until her admission to the hospital. Blurring of vision set in one week prior to her admission to the hospital and on the day of admission nosebleeds began.

Physical Examination.—The patient was pale, slightly emaciated and obviously critically ill. Scattered over the body were isolated purpuric spots and ecchymotic areas. There was a patchy brown discoloration of the neck and abdomen, which may have been due to previous arsenic therapy. The Rumpel-Leede capillary resistance test was strongly positive after five minutes. There were dry clots of blood in the nares. Numerous hemorrhagic spots, some with distinct white centers, were seen in the fundi. The retinal venules were distended and tortuous, and the nerve borders were indistinct. There were dry, crusted, ulcerative lesions at the angles of the mouth. The oral mucous membranes were boggy, and desquamation was easily produced by wiping. The tonsils were swollen and edematous and had the appearance that is occasionally seen preceding ulceration. Generalized lymphadenopathy was present, but the nodes were only moderately enlarged. There was a systolic murmur audible over the entire precordium. The lower border of the spleen was felt 4 fingerbreadths and the edge of the liver 2 fingerbreadths below the costal margin.

Laboratory Examinations.—There were 770,000 red blood cells and 46,250 leukocytes per cubic millimeter. The hemoglobin value was 15 per cent, of 15.4 Gm. A differential count showed 1 per cent neutrophils, 6 per cent lymphocytes, 31 per cent monocytes and 62 per cent "blasts," probably monoblasts. Fluctuations in the number of leukocytes are charted in figure 2. Cells identified as clasmatocytes (Sabin) were present in proportions varying from 1 to 14 per cent of the total number of leukocytes. The clasmatocytes were the largest cells seen in the fixed and supravital preparations. Fixed with Leishman's stain, they were seen to vary from 18 to 30 microns in diameter. The nuclei were constantly reniform or horseshoe shaped. The granules, which were ordinarily not numerous, were arranged about the nucleus, usually in the *Hof*. A photomicrograph of a smear is presented in figure 1 *B*.

Supravital examinations and differential counts by this technic were made at repeated intervals during the course of the illness. The appearance, motility and behavior toward neutral red and janus green of the monocytic elements was similar to that described in previous cases.[7] The clasmatocytes were identified by their greater size, their horseshoe or reniform nuclei and the irregular distribution of the neutral red vacuoles the hue of which was more variable than that of the monocytes. No distinction in regard to motility could be made. Particles of janus green were not evident in the clasmatocytes. After several blood transfusions phagocytosed, crenated red blood cells were commonly seen in both clasmatocytes and monocytes.

As indicated in figure 2, there was a gradual fall in the total number of leukocytes. This was accompanied with a complete disappearance of cells of the granulocytic series and a gradual drop in the actual and relative numbers of monocytic elements. The number of cells of the lymphocytic series fluctuated only slightly throughout the course of the illness.

Hemolysis appeared in a 0.44 per cent saline solution and was complete in a 0.34 per cent solution. The limits in a normal control were 0.44 per cent and 0.36 per cent, respectively. The patient's blood was in group 1, according to the classification of Jansky. The bleeding time was two minutes and forty seconds.

7. Dameshek.[3] Clough.[4]

The clotting time by the capillary tube method likewise was two minutes and forty seconds. There were from 30,000 to 150,000 platelets per cubic millimeter of blood. From 20 to 30 per cent of the leukocytes contained granules that showed a positive reaction to the Goodpasture peroxidase stain.

The Kahn test was negative. The heterophile antibody agglutination test was negative. Blood cultures were sterile until shortly before the patient's death, when Bacillus coli was obtained. Staphylococci, Micrococcus catarrhalis, a hemolytic strain of Staphylococcus albus and hemolytic streptococci were obtained from cultures of sputum.

Except for small amounts of albumin, the urine was normal. There was no Bence-Jones protein in the urine. The feces were normal.

Clinical Course.—The temperature was continually high, ranging between 101 and 105.5 F. The pulse rate fluctuated between 105 and 160. Despite eight blood

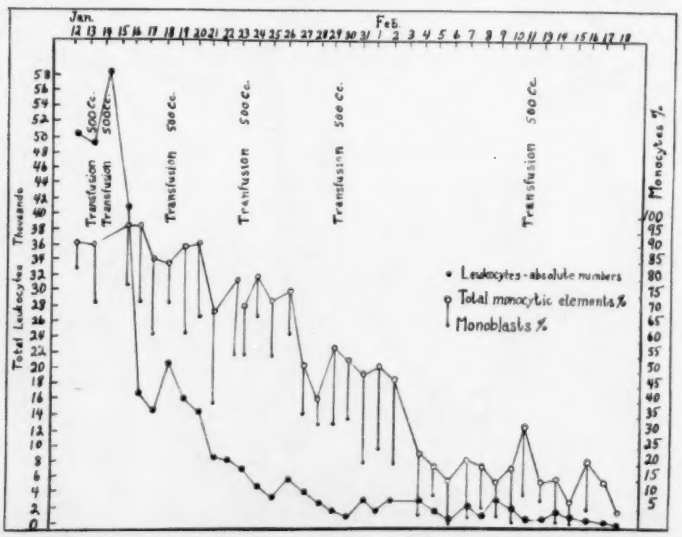

Fig. 2 (case 2).—Fluctuations in the number and percentage of leukocytes in a case of monocytic leukemia. Note the terminal leukopenia.

transfusions, the patient's condition steadily grew worse. Shortly after her admission to the hospital deafness and signs of bilateral acute otitis media developed. A cough productive of blood-tinged sputum and signs of bronchopneumonia appeared. The lesions at the angles of the mouth developed slowly into deep, necrotic ulcers with a dirty, grayish yellow base and only slight surrounding inflammation. Similar necrotic ulcers developed in the soft palate and anus. Cultures of material from these lesions contained a heterogeneous growth of organisms, which included spirilla and fusiform bacilli. On the thirty-seventh day of hospitalization the patient died. The total duration of the illness was approximately seven months.

Necropsy.—There were scattered petechial hemorrhages into most of the tissues and serous surfaces.

There was generalized enlargement of the lymph nodes. On section they were deep red-brown. The general architecture of the lymph nodes was moderately well preserved. The striking picture seen in all the nodes was that of infiltration with large numbers of mononuclear phagocytic cells containing red blood cells and blood pigment. The sinusoids and capillaries were distended with these cells, and the surrounding loose fatty tissue likewise was invaded. There was a definite increase in the amount of fibrous connective tissue.

The spleen weighed 345 Gm. The surface was deep red on section, and malpighian bodies and trabeculae were discernible. There was a diffuse infiltration of large mononuclear phagocytic cells containing golden brown pigment and red blood cells. Small amounts of pigment lay free in the tissue spaces. The malpighian bodies were for the most part small. There appeared to be a diffuse increase in the amount of reticular connective tissue.

The liver weighed 1,785 Gm. The cut surface was light brown, mottled with yellow and red, and the lobulations were readily seen. For the most part the hepatic cords were well preserved; in some zones the cells were vacuolated. The veins and sinusoids were distended with large mononuclear cells. In some of the portal zones the connective tissue appeared loose and edematous, and there was a slight increase in the amount of fibrous connective tissue. Figure 3 *A* is a photomicrograph of a section of the liver.

The tibial marrow was relatively aplastic. There was much fat, and the venous channels were widely dilated with blood. The marrow from the sternum showed a striking absence of myeloid elements. Whether or not young myelocytes and myeloblasts were present could not be determined. Mononuclear cells, probably monocytes, were present. Cells of erythroblastic series, notably erythroblasts and normoblasts, were present in small numbers. The absence of myeloid cells was in keeping with the clinical picture of a continuously decreasing leukocyte count, which fell finally to less than 1,000 cells per cubic millimeter.

In a preparation from the rectum was noted a loss of the normal mucosa, and the tissue in this region was necrotic, opaque and amorphous. Below this zone the tissue was infiltrated by mononuclear cells, round cells, plasma cells and polymorphonuclear cells, and fibroblastic proliferation was evident.

There was organizing and necrotizing focal pneumonia of the lungs. In some areas large phagocytic cells with vesicular nuclei and abundant cytoplasm, containing red and white blood cells, were conspicuous.

There was hemorrhage into the left middle ear and a thin, yellow exudate was present in the region of the middle ear both on the left and on the right.

No cellular infiltration of the heart, pancreas, adrenal glands, kidneys or thyroid gland was evident.

Case 3.—H. G., a 12 year old white American schoolboy, was admitted to the New Haven Hospital because of fever. The child was born at full term, weighing 7½ pounds (3,400 Gm.), and the delivery was normal. He had measles, mumps, whooping cough, chickenpox and at 12 months a convulsion the cause of which was not determined. He had been vaccinated for smallpox. The Schick test was negative.

Three weeks before his admission to the hospital a slight loss of appetite, constipation, drowsiness and pallor were first noticed. He complained of weakness and a dull constant pain in the right upper quadrant of the abdomen. Two weeks before his admission to the hospital a pain, interpreted as a toothache, developed on both sides of the lower jaw. Because of this a tooth was extracted on the day before his admission to the hospital.

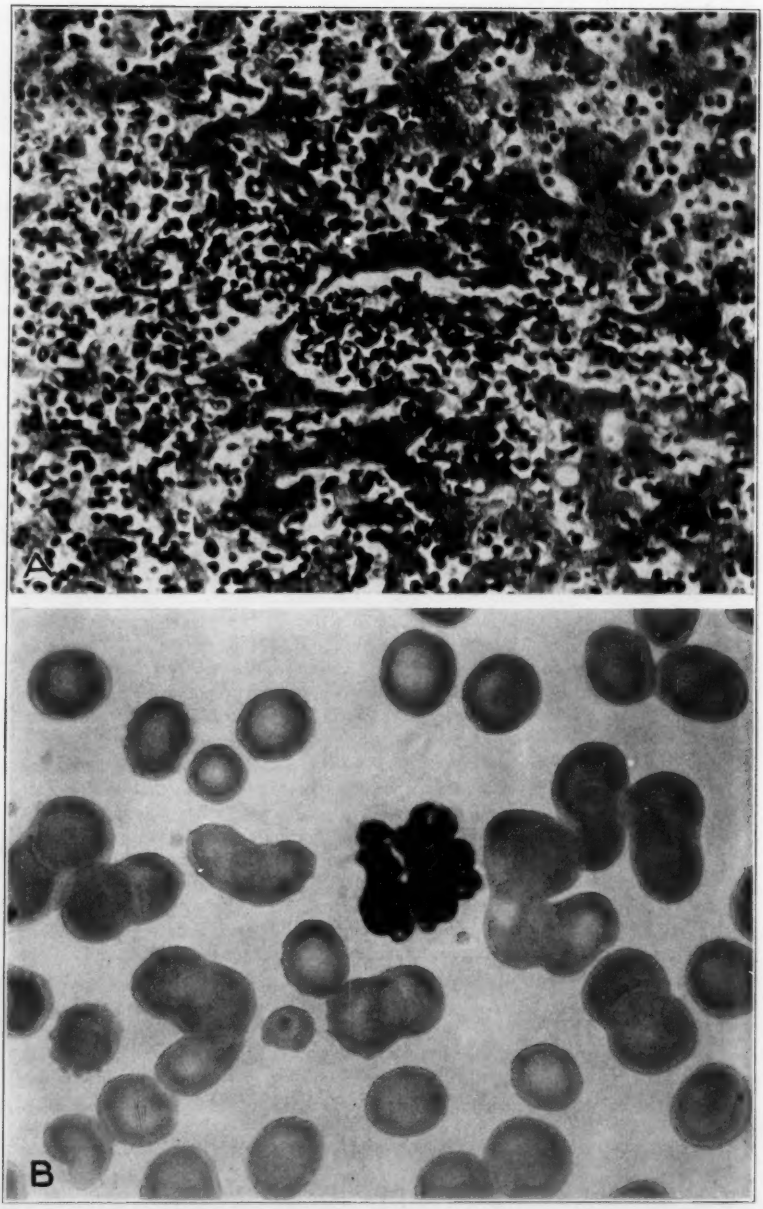

Fig. 3.—*A* (case 2), photomicrograph of a section of the liver; × 250. Note the massive infiltration with mononuclear cells, causing atrophy and destruction of the hepatic cords and an increase in the amount of connective tissue. *B* (case 7), photomicrograph of an unusual leukocyte from a patient with monocytic leukemia; × 1,125. Note the segmentation of the nucleus into a radial grapelike cluster of densely stained lobes. The cytoplasm is delicately stained and contains no granules. A large vacuole is discernible, and the irregular scalloped outline of the cell can be detected.

Physical Examination.—The boy was pale and looked sick. There were a few petechiae in the skin. The gums were swollen, red and tender. There were hemorrhagic spots on the tongue and soft palate. The breath had a foul odor. The tonsils were injected and extraordinarily large. There was slight generalized lymphadenopathy, but only the cervical lymph nodes were markedly enlarged; those at the angles of the jaw were approximately 4 cm. in the long diameter. Examination of the eyes revealed globular and flame-shaped subhyaloid and preretinal hemorrhages in the fundi. There was a systolic murmur best heard at the base of the heart. There was diffuse tenderness on palpation of the abdomen. The edge of the spleen was felt 3 fingerbreadths and the liver 2 fingerbreadths below the costal margin.

Laboratory Examination.—The hematologic data are given in table 1. The cells of the monocytic series ranged from fully mature specimens with horseshoe-shaped nuclei to young monoblasts containing one or more nucleoli. The borders of the adult cells were frequently irregular in outline and sometimes scalloped; occasionally actual pseudopodia were seen. The essential characteristics of the cells conformed precisely with those previously described.

TABLE 1.—*Data on the Blood in Case 3*

Date	Erythrocytes, Thousands	Hemoglobin, %	Leukocytes	Differential Count, Leishman Stain			
				Neutrophils, %	Lymphocytes, %	"Blasts," %	Monocytes and Monoblasts, %
7/29	1,900	40	6,100				
7/30	2,600	46	13,700				
7/31	2,200	47	12,500	10	10	1	79
8/ 1	2,200	44	28,000	5	7	2	86
8/ 2	1,900	42	29,500	1	25	..	74
8/ 3	1,900	40	40,600	..	15	..	85
8/ 4	1,700	40	67,000	2	25	..	73
8/ 5	900	30	78,800	2	23	..	75
8/ 6	1,800	40	75,200	4	10	..	86

There were slight poikilocytosis and anisocytosis and occasional stippling of the red blood cells. The reticulocyte count varied from 3 to 0.2 per cent. From 390,000 to 410,000 platelets per cubic millimeter of blood were present. The bleeding time increased from three minutes on August 3 to ten minutes on August 5. The clotting time remained between two and four minutes. The heterophile antibody agglutination test was negative. The Kahn test was negative. The blood was in group 2, according to the Jansky classification. Blood culture was sterile.

The reaction to the tuberculin test was negative in all dilutions. The Schick test showed a positive reaction. Culture of material from the nose contained staphylococci and diphtheroids, and the usual flora, including hemolytic streptococci, were grown from material from the throat. There were occasional waxy casts, many large granular casts and albumin in the urine (1 plus).

The spinal fluid contained 7 leukocytes and 165 red blood cells per cubic millimeter. Stereoroentgenographic examination of the chest revealed unusually prominent hilar regions, probably owing to enlarged paratracheal nodes, and there was also an increase in the coarseness of the markings throughout both pulmonary fields.

Clinical Course.—There were daily fluctuations of temperature within the limits of 100.5 and 105 F. The lymph nodes, liver and spleen rapidly increased in size, the spleen finally extending below the level of the umbilicus. Ulceration of

the gums developed and spread to the lower lip and the anterior faucial pillars. These mucous membranes became necrotic and foul smelling and were covered by a dirty gray membrane. Edema of the face appeared. This was apparently associated with the necrosis of the mucous membranes of the mouth. There were massive hemorrhages into the eyegrounds, with detachment of the retina of the right eye. On his ninth day in the hospital the patient died. The total duration ot the illness was approximately thirty days.

Necropsy.—There were numerous petechial hemorrhages into all the serous surfaces of the body and large and small hemorrhages into all the tissues of the body.

The spleen weighed 790 Gm. The cut surface was deep red and was peppered with enlarged, deeply purple malpighian bodies. Under the microscope it was seen that this appearance was due to the extensive extravasation of blood into the malpighian bodies. The normal architecture of this organ was obliterated. The sinusoids were distended, and the pulp was crowded with large round, oval or irregularly polyhedral cells with large eccentrically placed nuclei. The nuclei were oval, indented or folded over and hyperchromatic. The cytoplasm was slightly basophilic. Some of these cells contained acidophilic and others basophilic granules. An occasional mitotic figure was seen. In addition there were many cells resembling those of the myeloid series of the blood.

The liver weighed 1,600 Gm. The usual architecture was indistinct. The sinusoids were filled and markedly distended with mononuclear cells. The hepatic cords were narrowed owing to the crowding of the sinusoids, and in some zones the hepatic cells were necrotic, containing pyknotic nuclei. This was particularly evident in the periportal regions, where the cellular infiltration was most striking. The Kupffer cells in some zones appeared swollen. There was no increase in the amount of fibrous connective tissue.

All the abdominal, peritracheal and peribronchial lymph nodes were enlarged and deep red. When sectioned the cut surfaces were deep red, with small, scattered zones of yellow-white tissue. The usual architecture was almost completely effaced, and the follicles were obliterated. The sinusoids and surrounding tissues were heavily infiltrated with the characteristic mononuclear cells. Occasional mitotic figures were seen. Moderate numbers of small lymphocytes, a few neutrophils and eosinophils and an occasional large phagocytic cell also were present.

The bone marrow was hyperplastic, appearing red-brown. On section of the sternal marrow, hyperplasia of cellular elements was evident. There was great infiltration of the marrow with monocytes. While most of these cells appeared to be mature and most of the cells were identifiable, there were some smaller, less differentiated cells which were possibly reticular cells. Erythropoiesis was apparently normal, although it was not a striking part of the picture. Numerous myeloid cells in all stages of development, but with a preponderance of the more mature types, were present.

There was extensive invasion and infiltration with mononuclear cells of the heart, lungs, pancreas, adrenal glands, kidneys, thyroid gland, intestines, tonsils and other organs of the body. Areas of ulceration were present in the intestines, and on microscopic examination these were seen to be due to extensive invasion with the same cells.

CASE 4.—W. H., a 56 year old white American farmer, married, was admitted to the Grace Hospital because of superficial injuries sustained one week before. He had been in good health until one month before his admission to the hospital,

when spontaneous suppurating ulcers appeared on the lateral aspect of the right thigh and ankle. He went to the New Haven Dispensary, where a diagnosis of leukemia was made on the basis of the examination of the blood, which showed: red cells, 3,700,000; hemoglobin, 90 per cent (Dare), and leukocytes, 8,600, of which 7 per cent were neutrophils, 31 per cent lymphocytes and 62 per cent monocytes. Except for the local lesion, the physical examination revealed no abnormality. The patient refused to enter the hospital.

The previously described ulcers healed promptly, but three weeks before the patient's admission to the hospital a similar persistent ulcer appeared on the left ankle after trauma. One week before his admission to the hospital the patient was injured by a cow and was admitted because of pain, weakness and fever subsequent to the accident.

Physical Examination.—The patient was emaciated. There were superficial bruises of the thorax. A few purpuric spots were diffusely present on the skin. Over the left external malleolus there was a suppurating ulcer. At the mucocutaneous junction of the mouth on the right side there was an ulcer about 5 cm. in diameter covered with a dry brown crust. There were a few recent retinal hemorrhages. The teeth were all missing and the gums were not remarkable. There was slight inflammation of the pharynx. The cervical lymph nodes were slightly enlarged, but there was no other lymphadenopathy. There were signs of emphysema of the lungs. The edge of the liver was palpable, but the spleen could not be felt.

TABLE 2.—*Data on the Blood in Case 4*

Date	Leukocytes	Neutrophils, %	Lymphocytes, %	Monocytes and Monoblasts, %
8/ 3	8,800	0	10	90
8/ 4	23,000	1	10	89
8/ 7	61,000	2	8	90
8/ 8	70,000	2	13	85
8/ 9	88,000	3	8	89
8/10	118,000	1	9	90
8/11	265,000	2	8	90
8/12	328,000	0	8	92

Laboratory Examination.—The cells of the monocytic series were large and had abundant clear blue cytoplasm. Fine azure granules were present in the older forms, and in some of these there were vacuoles. Pseudopodic projections were numerous. The nuclei were leptochromatic and round, kidney shaped or actually lobulated. The proportion of cells classified as "blasts" increased rapidly, and in many of these there were nucleoli.

On the patient's admission to the hospital there were 4,400,000 red blood cells, and the hemoglobin value was 75 per cent, according to the Sahli standard. A reduction in the number of blood platelets was evident from an examination of stained smears. The erythrocyte count fell to 4,000,000 and the hemoglobin content to 62 per cent before death occurred.

Blood culture was sterile. The Wassermann reaction was negative. Bacillus pyocyaneus was recovered from the malleolar ulcer. On roentgen examination of the thorax enlargement of the hilar shadows and a localized area of rarefaction of the seventh rib on the left were noted.

Clinical Course.—The temperature was 100 F. when the patient was admitted to the hospital. Thereafter there were wide daily fluctuations with peaks as high as 104 F. Symptomatic treatment was of no avail, and the patient failed rapidly.

Five days before death the spleen became palpable. Nine days after admission to the hospital the patient died. The duration of the illness was slightly more than one month.

Necropsy.—There were hemorrhages of varying extent into the skin, the organs of the body and the serous surfaces.

All the lymph nodes were enlarged and relatively soft in consistency. On section of a mediastinal node obliteration of the normal architecture was evident. The surface appeared mottled, and multiple hemorrhages were visible. A cavity approximately 1 cm. in diameter, apparently the result of a previous hemorrhage, was seen. Diffuse, massive infiltration with large cells containing round, oval or reniform nuclei with a fine chromatin network and clear-staining cytoplasm was evident microscopically.

The spleen weighed 235 Gm. The cut surface was soft, pale gray and dotted with small areas of hemorrhage. The normal structure was obliterated by the massive invasion of cells the characteristics of which have been previously described.

The liver weighed 1,860 Gm. The surface was smooth, friable and mottled. Microscopically there were seen many small islands of the typical cells, and these were present also in considerable numbers between the columns of hepatic cells.

There was a striking decrease in the amount of normal fat in the bone marrow. Slight hyperplasia of the reticular tissue was evident. The normal cells of the bone marrow were displaced by an extensive uniform infiltration of large cells. These were characterized by their size and by large vesicular leptochromatic nuclei which were occasionally round but predominantly irregular or horseshoe-shaped. The cytoplasm was abundant, and only rarely were granules or vacuoles seen. Phagocytosis of cell fragments and pigment by these cells was occasionally seen. There was a scattering of eosinophils.

Cells of the myeloid series were only rarely encountered. Red blood cells were more abundant, but few normoblasts and megaloblasts were present. A scattering of blood platelets but no megalokaryocytes were seen.

The heart weighed 320 Gm. There were numerous subepicardial hemorrhagic spots, and in the pulmonary artery there was a large, jellylike grayish white thrombus which on microscopic examination was seen to be composed of a mass of monocytic cells bound together by small amounts of fibrin.

Infiltration with cells of the monocytic series was evident in the lungs, kidneys, adrenal glands and gastro-intestinal tract.

Case 5.—S. C., a 60 year old white widow, a housewife and practical nurse, entered the New Haven Hospital because of increasing weakness of six months' duration. In 1911 the patient had been operated on for strangulated hernia. Six months before the present admission to the hospital she fell, struck her head and lost consciousness. She dated her illness from this fall. Three months before her admission to the hospital, following a sore throat, rapidly progressing weakness and pallor were noted, and purpuric spots began to appear on the trunk and extremities. At this time fever developed and continued intermittently. Blurring of vision had been noted for four days, and two days before entering the hospital the patient became too weak to leave her bed.

Physical Examination.—Pallor and cyanosis were striking. Numerous purpuric and petechial spots were present over the entire body. There was a large subconjunctival hemorrhage in the left eye. There were numerous retinal hemorrhages, some of which had white centers. The mouth was edentulous, but there were many small hemorrhages into the soft palate. The cervical, axillary and inguinal lymph nodes were slightly enlarged. There was dulness, with moist râles at the

bases of the lungs. The area of cardiac dulness was moderately increased, and a systolic murmur was heard. The blood pressure was 130 systolic and 80 diastolic. The edge of the liver was felt about 1 cm. and the spleen about 5 cm. below the costal margin.

Laboratory Examination.—The blood was in group 3, according to the Jansky classification. The Kahn test was negative. The urine was normal, except for a slight trace of albumin.

The red blood cell count was 1,400,000 per cubic millimeter, and the hemoglobin value was 20 per cent, of 15.4 Gm. There were 203,000 leukocytes per cubic millimeter, of which 2 per cent were neutrophils, 32 per cent lymphocytes, 53 per cent monocytes and monoblasts, 2 per cent eosinophils, 1 per cent clasmatocytes (Sabin) and 10 per cent undifferentiated cells.

The predominant cells were large, and all stages of development from the youngest monoblast to the mature monocyte were present. The outline of the older cells was often irregular. The cytoplasm of all the cells was abundant and stained a hazy powder blue. Occasional Auer bodies were present in the immature cells. The cytoplasm of the older cells contained a variable number of fine azurophilic granules. The nuclei of the monoblasts were round or oval, and many contained nucleoli embedded in a homogeneous network of chromatin. The more mature cells were characterized by typical oval or hroseshoe-shaped nuclei. In some the nucleus was distinctly irregular and sometimes lobed. No evidence of phagocytosis was seen.

Clinical Course.—The temperature was 102 F., the pulse rate 100 and the respiratory rate 24. The patient was moribund when admitted to the hospital and shortly afterward lapsed into unconsciousness. In twelve hours she died. The duration of the disease was approximately six months.

Necropsy.—There were numerous petechial hemorrhages into the skin, mucous membranes, pleurae, diaphragm, liver, spleen and bladder. The lymph nodes throughout the body were slightly enlarged, and the surfaces were deep red on section. The usual architecture was distorted by large numbers of mononuclear cells, which filled the capillaries and sinusoids. These cells contained large oval or bean-shaped, eccentrically placed nuclei. The cytoplasm was abundant. There was a slight general increase in the amount of reticulum.

The spleen was moderately firm and weighed 530 Gm. In some places the capsule was thickened, owing to infiltration with mononuclear cells. The usual architecture was distorted; the malpighian bodies were indistinct, but the trabeculae were prominent. The splenic pulp was filled with the previously described large mononuclear cells. There was no increase in the amount of interstitial connective tissue.

The liver weighed 2,025 Gm. The usual architecture was preserved. The sinusoids and periportal zones were crowded with large mononuclear cells. The cells of the hepatic cords were not always clearly distinguishable.

A section of the vertebral marrow gave evidence of extensive invasion by small round cells. The normal hematopoietic tissue was almost completely obliterated by the process. The predominant cells were somewhat larger than normal mature small lymphocytes. The distribution of the chromatin resembled that often seen in lymphocytes, but the density of the nuclear staining was lighter than that of mature lymphocytes. In the majority of the cells the cytoplasm was basophilic, and often the amount was small. These cells, which had the appearance of immature elements, resembled the cells of the general reticulum, with varied

morphology and a tendency toward the formation of delicate cytoplasmic processes and occasionally syncytial sheets. They contained no phagocytosed material or vacuoles. No macrophages were seen.

Sections of the bone marrow were submitted to Dr. R. P. Custer, of Philadelphia, who concurred in the general interpretation and in the diagnosis of monocytic leukemia.

Case 6.—E. V., a white boy aged 16, entered Grace Hospital because of weakness. Seven months before his admission to the hospital he had begun to notice general malaise and easy fatigability. This continued for several months but was not severe enough to keep him from playing baseball and football. Two months before his admission to the hospital he injured his left knee and began to limp. This was followed by spontaneous migratory pain in the right knee and both shoulders. No swelling, redness or local heat was noted in the joints. Seven weeks before admission to the hospital he had a severe toothache, high fever and sweats. He also began to lose weight about this time and felt sick enough to

Table 3.—*Data on the Blood in Case 6*

Date	Hemoglobin, %	Erythrocytes, Thousands	Leukocytes	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Comment
12/13/33	20	1,130	2,600	45	48	5	2	
12/14/33	Transfusion, 500 cc.							
12/15/33	30	1,840	3,200	48	40	10	2	
12/18/33	Transfusion, 500 cc.							
12/18/33	..	.....	51,200	18	22	58	2	
12/19/33	..	.....	57,200	13	30	57	..	
12/21/33	..	.....	78,800	19	22	59	..	
12/26/33	50	3,140	105,000	12	53	35	..	Peroxidase: 98% negative, 2% positive; platelets 240,000
12/27/33	Transfusion, 500 cc.							
12/28/33	50	2,980	37,000	11	58	31	..	
12/31/33	50	3,010	14,800	27	52	21	..	
1/ 2/34	..	.....	13,800	10	51	37	..	
1/ 4/34	50	3,040	21,000	5	63	32	..	
1/ 6/34	Transfusion, 500 cc.							
1/ 8/34	50	3,640	25,200	7	70	23	..	
1/11/34	50	2,050	63,600	2	18	80	..	
1/15/34	40	1,890	52,800	6	23	71	..	
1/18/34	50	3,160	78,600	6	38	56	..	

remain in bed. Two weeks before his admission to the hospital a tooth was removed, and this resulted in copious hemorrhage from the socket and persistent oozing for twelve days. From this time on he became much weaker, and pallor developed. There were periods of delirium. The past history revealed only penumonia in 1932, an appendectomy in 1923 and "growing pains" as a child. The patient's mother had had tuberculosis, but no roentgen evidence of this process was noted in the patient or in other members of the family.

Physical Examination.—Marked pallor and petechiae of the skin were noted. Emaciation was evident. The breath had a fetid odor. Retinal hemorrhages were present in the eyes. The gums were ulcerated and bleeding. The cervical and inguinal lymph nodes were enlarged, those of the anterior cervical chain having attained the size of pigeon eggs. There was hypertrophy of the heart, and a gallop rhythm and a to and fro murmur were heard at the apex. The lungs were normal, but there was elevation of the diaphragm on both sides. Both the liver and the spleen were large and extended downward to about the level of the umbilicus.

Laboratory Examination.—A fairly advanced picture of hypochromic anemia with poikilocytosis, anisocytosis and polychromatophilia was seen. Platelets were

present in a greatly reduced number. A few normoblasts were seen. The monocytes were large cells which varied in size but averaged more than 16 microns in diameter. Practically all the cells were typically mature elements. The outline of the cells was often irregular, and in many instances actual pseudopods were apparent. The cells had abundant cytoplasm, in which were seen numerous fine azure-staining granules, for the most part grouped in the indentations of the nuclei. The nuclei were round, kidney shaped or actually lobulated. The chromatin network was delicate and evenly distributed. Nucleoli were seen only rarely. Cells that could be identified as clasmatocytes were not seen.

Biopsy of a large cervical lymph node revealed complete obliteration of the normal architecture by a massive infiltration of large round cells, with abundant cytoplasm and nuclei, which were round, kidney shaped or lobulated. These cells resembled closely the predominant cells of the peripheral blood.

Examination of the urine and feces revealed no abnormality. One blood culture showed Staphylococcus aureus, but this was thought to be due to contamination, because several later cultures proved sterile. Roentgenograms of the chest showed no abnormality. The bleeding and the clotting time were normal. The nonprotein nitrogen content was 38 mg. per hundred cubic centimeters of blood. The Kahn and Wassermann tests were both negative.

Clinical Course.—Solution of potassium arsenite was administered, and four blood transfusions were given. At first the size of the lymph nodes seemed to decrease under treatment, but later they returned to the original size. The spleen and liver remained about the same. The temperature was irregular and of the "steeple" type but was constantly high. The general course was steadily downhill. The patient left the hospital against advice and died about three weeks after discharge. The total duration of the illness was approximately nine months.

Case 7.—C. E., a 62 year old Italian widow, entered the New Haven Hospital because of weakness and fever. She was known to have had elevation of the blood pressure for ten years. Beginning approximately two months before her admission to the hospital, weakness and progressive loss of weight were noted. During this period she lost about 20 pounds (9 Kg.). One week before admission to the hospital she became unconscious for about ten minutes and fell to the floor. Subsequently she felt extremely weak, was feverish and complained of pain in the lower portion of the left side of the chest and neck.

Physical Examination.—Malnutrition and dehydration were marked, and there was pallor of the skin and mucous membranes. The gums were boggy and red. The cervical lymph nodes were firm and slightly enlarged; other glands were not remarkable. Arteriosclerotic changes were evident in the retinal vessels and the peripheral arteries. There was a pleural friction rub, and signs of bronchopneumonia were noted at the base of the left lung. The heart was enlarged; the left border of cardiac dulness was in the anterior axillary line in the fifth interspace. A systolic murmur was heard over the entire precordium. The blood pressure was 120 systolic and 80 diastolic.

The abdomen was intensely distended, but both the liver and the spleen were moderately enlarged, and they were palpated below the costal margin.

Laboratory Examination.—Hematologic data are shown in table 4. The cells classified as clasmatocytes varied in size. Some were no larger than the ordinary monocyte, but the majority were the largest cells seen and ranged from 20 to 30 microns in diameter. The outline of these cells was irregular and scalloped, and in some there were actual pseudopodia. The cytoplasm was a delicate pale blue with Leishman's stain and contained occasional vacuoles but few if any granules. The

nucleus was segmented into from two to twenty lobes connected by delicate strands and arranged in a radial cluster that resembled a bunch of grapes. The chromatin was condensed into irregular, heavy blotches which stained extraordinarily densely. In figure 3*B* a photomicrograph of one such cell is presented. On supravital study with neutral red and janus green these cells were seen to be motile, changing form more rapidly than the monocytes present. However, progression was slow, and in this particular they differed sharply from the neutrophils. The clasmatocytes contained many neutral red particles or vacuoles of various hues which ranged in size from small granules to bodies half as large as a lobe of the nucleus. Only an occasional janus green granule was seen.

When trypan blue was added to blood in vitro about 50 per cent of the cells took up the dye. Those classified as clasmatocytes contained an abundance of blue granules and vacuoles similar in size and configuration to the neutral red bodies.

As the disease progressed and the predominant cells became more immature, the percentage of cells taking up the dye decreased and the amount of dye in the

TABLE 4.—*Data on the Blood in Case 7*

Date	Erythrocytes, Thousands	Hemoglobin, %	Leukocytes	Differential Count, Leishman Stain						Comment
				Neutrophils, %	Lymphocytes, %	Mononuclears, %	Myelocytes, %	Monoblasts, %	Clasmatocytes, %	
12/ 7	2,500	60	10,000	..	..	..	..	..	..	
12/ 8 a.m.	.....	..	11,000	1	8	25	3	20	43	
12/ 8 p.m.	2,700	55	13,200	..	..	..	..	..	..	
12/ 9	2,000	52	25,600	..	..	..	..	..	..	
12/10	2,000	45	.....	2	6	..	..	63	29	
12/ 8	.....	..	.....	12	14	..	8	..	..	Supravital differential count: monocytes monoblasts and clasmatocytes, 66
12/ 9	.....	..	.....	2	16	..	26	22	34	

cells grew more scant. The monocytes had the usual motility and rosette arrangement of neutral red vacuoles. Many of the predominant cells, clamatocytes and monocytes, took the peroxidase stain. There were anisocytosis and poikilocytosis of the erythrocytes, with occasional macrocytes and normoblasts.

The urine contained albumin (1 plus) and from 10 to 13 white blood cells per high power field. The feces were normal.

Stereoroentgenographic examination of the chest revealed elevation of the diaphragms, thickening of the pleurae and the presence of pleural effusion at the base and between the lower and the upper lobe of the left lung. There was evidence of a tumor in the upper portion of the mediastinum, with displacement of the trachea to the right.

The Kahn serologic test was negative. The nonprotein nitrogen content was 52 mg. per hundred cubic centimeters of blood.

Clinical Course.—The patient appeared chronically ill when admitted to the hospital. The temperature fluctuated between 102 and 105 F., the pulse rate between 110 and 140 and the respiratory rate between 22 and 40. Distention was intractable. Four days after admission to the hospital the patient lapsed into coma, and he died on the next day. Treatment had been entirely symptomatic. Permission for necropsy was not granted.

Although symptoms had been evident to the patient for only two months, it was thought probable that the duration of the disease had been appreciably longer. This case was unique in that there was a high percentage of cells identified on fixed smear and supravital studies as clasmatocytes.

CASE 8.—M. H., a 74 year old white American widow, was referred by Drs. William Dennehy and Wilder Tileston. Early in June 1934 following removal of a tooth the patient's gums became swollen and ecchymotic, the inflammation extending to the cheek and neck of the affected side. The process was slow to subside, but after about three weeks the patient seemed entirely well again. Toward the end of July rapidly progressing weakness appeared, and the patient was forced to go to bed. Her appetite began to fail about this time, and marked pallor and loss of weight were noted. About one week after going to bed she began to complain of sore throat and vague abdominal distress. Previous to the present illness the patient had always been exceptionally well. Her family history was interesting in that one brother had died of Addison's disease and another recently of leukemia.

Physical Examination—On Aug. 27, 1934, the patient was prostrate. Pallor was marked. The throat was red and edematous, but no ulcers were seen. The gums were not notable. The cervical lymph nodes were barely palpable, but there

TABLE 5.—*Data on the Blood in Case 8*

Date	Erythrocytes, Thousands	Hemoglobin, %	Leukocytes	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %
7/30	4,400	50	3,400			
8/14	4,400	50	23,000	5	20	75
8/21	3,000	45	120,000	5	10	85
8/26	.....	..	14,000			

was no generalized lymphadenopathy. The liver was enlarged and could easily be felt about 4 cm. below the costal margin. Although the spleen seemed large on percussion, it was not felt below the costal margin. The temperature was irregular in type, with a rise to 103 F. in the evening and a fall to 101 F. in the morning. The pulse rate was proportionately increased.

Laboratory Examination.—The predominant cells were large, with homogeneous, abundant cytoplasm that looked like ground glass. A few fine azure granules were present, and these were often grouped in the indentations of the nuclei. The nuclei were round, oval, kidney shaped or actually lobulated. The chromatin was finely woven and homogeneous. No nucleoli were seen. The characteristic cells seemed mature, and while there was some variation in this respect, none was seen that could be classified as a monoblast. There were many smudges present. Anisocytosis and poikilocytosis of the red blood cells were marked. Many macrocytes were seen and an occasional normoblast and rare megaloblast. The blood platelets were definitely decreased in number.

On supravital examination the characteristic pseudopodic activity and motion of the monocytes were evident. Cytoplasmic vacuoles were frequently observed. There was evidence of phagocytosis by these cells, and in one instance a monocyte was actually seen engulfing a red blood cell.

Clinical Course.—The patient failed rapidly and died on August 27. The course of the disease was probably between nine and twelve weeks.

COMMENT

The eight cases of monocytic leukemia herein reported were characterized by an abrupt onset of symptoms and a relatively short course. The average duration of life after the onset of symptoms was three and one-half months, with a range from one to nine months. Case 1 is the second recorded instance of monocytic leukemia in a Negro, a previous case having recently been reported by Levine.[5] The ages of our patients ranged from 12 to 74 years, the latter being the oldest on record. In five cases the symptoms were first noted following extraction of teeth and in two instances following severe trauma. In all eight cases the first symptoms appeared between June and October. Seven of the eight patients lived in the country.

There seemed to be an association between the degree of monocytosis and the duration of the illness. In the cases of fulminating monocytic leukemia the number of monocytes in the peripheral blood was great or else increased to high levels rapidly, whereas in those in which the disease progressed more slowly the absolute number of monocytes was only moderately elevated. In case 2, in which the course was relatively long, there was a progressive decline in the absolute number of monocytes so that terminally leukopenia actually prevailed. During the last weeks of the illness it would hardly have been possible to establish a diagnosis of monocytic leukemia from the blood picture.

In accord with most of the cases previously reported general enlargement of lymph nodes was only slight, and the cervical chains were principally involved. When cervical lymphadenopathy was prominent it was associated with ulcerative lesions of the oral cavity. It is a question whether such lymphadenopathy may not have been in part due to hyperplasia secondary to necrosis and infection of the regional tissue. The spleen was enlarged in seven of the eight cases, but in all instances hepatomegaly was prominent.

Contrary to the observations of some investigators,[8] one or more nucleoli were seen in many of the monoblasts. Peroxidase-positive granules were identified in a variable proportion of the monocytes. The extent of the anemia and thrombopenia with resulting hemorrhagic manifestations was similar in degree to that seen in other forms of acute leukemia. Examination of the hematolytopoietic tissues, either at biopsy or at necropsy, furnished information sufficient to confirm the diagnosis of leukemia, but for the accurate identification of the cell type concerned repeated examination of blood spreads fixed and supravitally proved of greater value.

8. Weissenbach, R. J.; Bourdillon, C.; Martineau, J., and David, J.: Leucémie aiguë à monocytes, Sang **7**:371, 1933. Fowler, W. M.: Monocytic Leukemia, J. Lab. & Clin. Med. **18**:1260 (Sept.) 1933.

COMPARATIVE DIURETIC RESPONSE TO CLINICAL INJECTIONS OF VARIOUS MERCURIALS

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An increase in the flow of urine is produced by suitable doses of any of the mercurial compounds that have been studied with this in mind, but for therapeutic use certain organic compounds are employed almost exclusively at present, largely in order to avoid other actions of mercury, which are practically inevitable with the inorganic mercurials. That the diuretic potency of the organic compounds is superior is probably often assumed, but without adequate evidence. The few quantitative clinical data are very inadequate, and quantitative comparisons on animals also are scanty, as may be seen from the review by Fourneau and Melville[1] (1931). These investigators confirmed with intravenous injections into rabbits the diuretic effect for all the inorganic and organic compounds of mercury which they tried, except colloidal suspensions, with quantitative differences that appeared related to the chemical constitution. Data on animals, however, cannot be transferred quantitatively to the clinic because of the difference in the dosage.

In our studies of the excretion of mercury in clinical treatment the urinary volume was always recorded, and thus a large number of data were accumulated, which seemed to furnish good material for a comparative study of diuretic potency. A preliminary report was made to the Federation of the American Biological Societies in 1930.[2] This report indicated not only that the flow of urine is increased by all forms of mercurial compounds used in the treatment of syphilis but that when

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1. Fourneau, E., and Melville, K. I.: Studies in Mercurial Chemotherapy: Concerning Mercurial Toxicity, Its Evaluation, Mechanism, and Relation to Chemical Constitution, J. Pharmacol. & Exper. Therap. **41**:21 (Jan.) 1931; Studies in Mercurial Chemotherapy: Quantitative Evaluation of Mercurial Diuresis and Its Relation to Chemical Constitution, ibid. **41**:47 (Jan.) 1931.

2. Sollmann, Torald, and Schreiber, Nora E.: The Diuretic Effects of Various Mercurial Treatments, Am. J. Physiol. **93**:689 (June) 1930.

the comparison is based on the dosage and especially on the excretion of mercury the inorganic mercurial salts appear vastly more potent than the organic compounds, so much so that it was suggested that the diuretic action of the organic mercurial compounds may be due to the dissociation of a small amount of ionizable mercury. In the meantime, considerable additional data have become available, including data on several compounds not mentioned in the first study. As we have now terminated our investigations of the excretion of mercury, it is opportune to review and coordinate the entire mass of data on diuretic potency.

It may be assumed that patients studied were not dropsical, as are most of those who are subjected to the induction of mercurial diuresis as a therapeutic measure. This, however, is an advantage for quantitative comparison; indeed, it is indispensable, for ascites would introduce the serious complicating factor of wide variations in the excretable tissue fluid. It must also be noted that the intake of water was not controlled, the patients being entirely free to take liquids according to their thirst. This is often a more suitable way of studying diuresis, as it tends to keep the water content of the organism automatically on a more uniform level than does an arbitrary intake of fluid, which could only by rare accident avoid either forcing or restricting the amount of fluid imbibed beyond this level. The ideal of uniform conditions of experimentation may easily overshoot its mark. In this case, a uniform intake of fluid, even if it is carefully adjusted to an equilibrium in the individual patient in a preceding period, takes no account of the extra loss of fluid in the diuresis or of the wide variations in the loss of water by the skin caused by changes in temperature, etc. A uniform intake of water may be needed for a study of special problems; in general, however, the consumption of fluid ad libidum appears to be better justified as well as more convenient. It is misleading only if the intake of water is artificially altered by some intercurrent condition, but accidental variations of this kind generally balance each other in different patients. The ad libidum consumption of fluid had a further special advantage in the present inquiry in that it simulates more closely the conditions in dropsy, in which the blood may "drink" freely from the water reservoir of the effusions.

Variations in the quantity of the flow of urine should be compared on the basis of the departure from normal, the surplus and the deficit, rather than on that of the total water balance, for inclusion of the normal urinary volume artificially "dilutes" or minimizes the changes. The increase or "surplus excretion" was calculated both in cubic centimeters and as a percentage of the normal output. As these lead to the same general conclusions, only the percentage basis is cited in comparison

of the data, for it is more rational and more consistent, an increase of 55 cc. being much more important when it is added to a normal value of 10 cc. than when it supplements one of 100 cc.

EXPERIMENTAL MATERIAL

The data were collected in our investigation of the excretion of mercury after intravenous and intramuscular injections.[3] The compounds may be grouped as follows, together with the dosage and intervals of administration and the number of patients and injections:

1. *Organic Compounds.*—Mercurosal (disodium hydroxymercurisalicyloxyacetate)[4]: Intravenous—three patients; from ten to twelve injections of 5 cc. of a 2 per cent solution (100 mg. of the compound, equivalent to 43.4 mg. of mercury) every second or third day.

Intramuscular—three patients; from ten to twelve injections of 2 cc. of a 2.5 per cent solution (50 mg. of the compound, equivalent to 21.7 mg. of mercury) every fourth or fifth day.

Novasurol (Merbaphen): Intravenous—two patients; four injections; first injection, 0.75 cc. of a 10 per cent solution (75 mg. of the compound, equivalent to 25.42 mg. of mercury), and subsequent injections, 1 cc. of a 10 per cent solution (100 mg. of the compound, equivalent to 33.9 mg. of mercury) once a week.

Intramuscular—three patients; from two to five injections; first injection, 0.75 cc. of a 10 per cent solution (75 mg. of the compound, equivalent to 25.42 mg. of mercury), and subsequent injections, 1 cc. of a 10 per cent solution (100 mg. of the compound, equivalent to 33.9 mg. of mercury) once a week.

Salyrgan: Intravenous—three patients; from three to four injections; first injection, 0.75 cc. of a 10 per cent solution (75 mg. of the compound, equivalent to 28.2 mg. of mercury), and subsequent injections, 1 cc. of a 10 per cent solution (100 mg. of the compound, equivalent to 37.6 mg. of mercury) once a week.

Intramuscular—three patients; from three to four injections; first injection, 0.75 cc. of a 10 per cent solution (75 mg. of the compound, equivalent to 28.2 mg. of mercury), and subsequent injections, 1 cc. of a 10 per cent solution (100 mg. of the compound, equivalent to 37.6 mg. of mercury) once a week.

2. *Inorganic Ionizable Compounds.*[5]—Mercuric Bromide: Intramuscular—three patients; from eight to ten injections; 0.25 cc. of a 4 per cent solution (10 mg. of the compound, equivalent to 5.5 mg. of mercury); three weekly injections followed by a series of injections, at first daily and finally spaced at longer and somewhat irregular intervals.

Bichloridol (Mercuric Bichloride in Oil):[6] Intramuscular—three patients; from five to seven injections; injections from capsules; exact content of mercury unknown, but not less than 4.8 mg. or more than 44.45 mg. of mercury; injections twice a week.

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3. Sollmann, Torald; Schreiber, Nora E., and Cole, H. N.: Excretion of Mercury After Clinical Intramuscular and Intravenous Injections, Arch. Dermat. & Syph. **32**:1 (July) 1935.

4. Mercurosal has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

5. This term is used rather loosely in the sense that the compounds yield reacting mercuric ions.

6. Bichloridol has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

Mercuric Oxycyanide: Intravenous—three patients; from six to seven injections; 5 cc. of a 0.2 per cent solution (10 mg. of the compound, equivalent to 8.55 mg. of mercury) twice a week.

3. *Inorganic Colloidal Compounds.*—Mercodel (Metallic Mercury):[7] Intravenous—three patients; four injections; first dose, 5 cc. of a 6 per cent solution (300 mg. of the compound, equivalent to 50 mg. of mercury); second and third doses, 10 cc. of a 6 per cent solution (600 mg. of the compound, equivalent to 100 mg. of mercury); fourth dose, 20 cc. of a 6 per cent solution (1,200 mg. of the compound, equivalent to 200 mg. of mercury); weekly intervals.

Mersulfol (Mercuric Sulfide):[8] Intravenous—three patients; from three to seven injections; 10 cc. of a 2 per cent solution (200 mg. of the compound, equivalent to 170 mg. of mercury) twice a week.

Intramuscular—five patients; from five to twelve injections; 3 cc. of a 2 per cent solution (60 mg. of the compound, equivalent to 51 mg. of mercury); first patient, 10 cc. twice a week for five injections; second patient, 10 cc. three times a week for one week and then 3 cc. per week for three weeks; three patients, 3 cc. two or three times a week.

4. *Unclassified Compounds.*—Flumerin: Intravenous—four patients; four injections; 10 cc. of a 2 per cent solution (200 mg. of the compound, equivalent to 65 mg. of mercury) once a week for four weeks.

Mercuric Salicylate in Oil Suspension: Intramuscular—three patients; four or five injections; 1 cc. of a 10 per cent solution (100 mg. of the compound, equivalent to 60 mg. of mercury) weekly.

Collection Periods.—The specimens of urine were collected uniformly for twenty-four hours before injection, and in the following periods after injection: up to one hour; from one to two, from two to four, from four to eight; from eight to sixteen, from sixteen to twenty-four, from twenty-four to forty-two, from forty-two to sixty-six hours, and then for twenty-four hour periods.

CORRELATION OF OBSERVATIONS AND DATA

To render the rather overwhelming mass of data manageable requires simplification and grouping whenever possible. The data are therefore presented as means, and the individual data are omitted, to avoid confusion and, incidentally, to economize on space. The hourly excretion in successive periods is a convenient starting point. Preliminary tabulations showed no marked trend in the diuresis caused by the successive weekly injections, and this makes it permissible to average the results of all the administrations of a given drug by a given channel. The hourly means may be most usefully presented in the form of curves, those for the intravenous injections in chart 1 and those for the intramuscular injections in chart 2. The time has been plotted logarithmically. The quantities, plotted vertically, are on a uniform scale for the urinary volume. The quantities of mercury varied through so wide a range that different decimal scales had to be employed, the magnification being

7. Mercodel has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

8. Mersulfol has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

indicated on each chart. Inspection of these charts gives considerable information on the general features of the problem.

1. The first glance reveals the striking qualitative directional similarity in practically all the curves between the urinary volume, the excretion of mercury and the concentration of mercury for all the different compounds and for intravenous and intramuscular injections. With a few minor exceptions, all the quantities reach the peak within one or two hours of the time of injection, and then descend as parabolic curves, with fairly comparable speed. The chief difference is in the height of the peaks, and for the curve of urinary volume this has the moderate

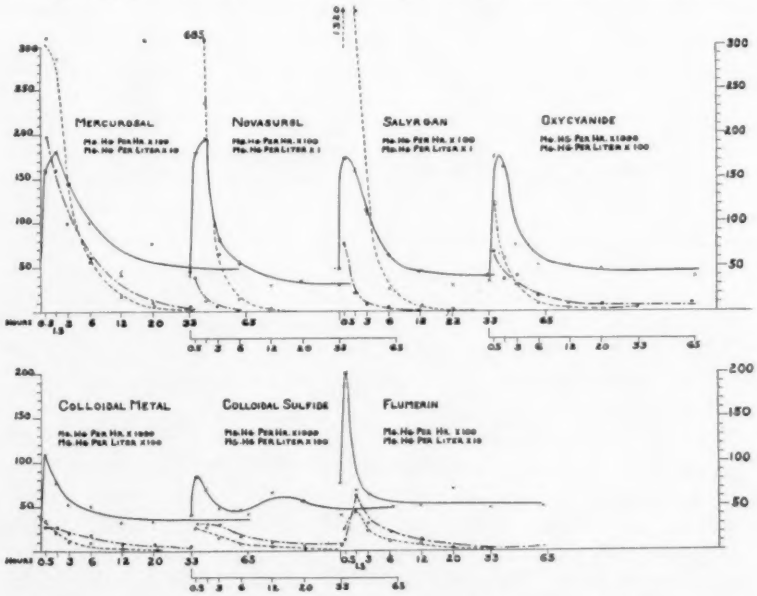

Chart 1.—Curves of means for output of urine and mercury after the clinical injection of various compounds of mercury intravenously. The notation is explained in the text. In this and the following charts the time in hours is plotted logarithmically, and the unbroken line indicates the urinary output in cubic centimeters per hour, the line of short dashes the number of milligrams of mercury per hour and the line of short and long dashes the number of milligrams of mercury per liter.

range of from 2 to 5 times the normal level. The differences are much greater in the curves for mercury because of the great difference in the doses.

2. The curves for the mean urinary excretion produced by intravenous and intramuscular injections are almost quantitatively identical

for most of the compounds, namely, salyrgan, mercurosal and the ionizable inorganic compounds. With novasurol the intramuscular injection causes a somewhat lower degree of diuresis; with colloidal mercuric sulfide the intravenous injection caused a distinctly lower degree of diuresis. It is notable that the diuresis caused by intramuscular injection is not materially slower than that caused by intravenous injection in any instance, but the excretion of mercury declines at a materially slower rate after intramuscular injection, at least with the organic compounds.

3. The diuretic effect of the therapeutic doses of the different compounds is of the same order of magnitude for all the organic and ion-

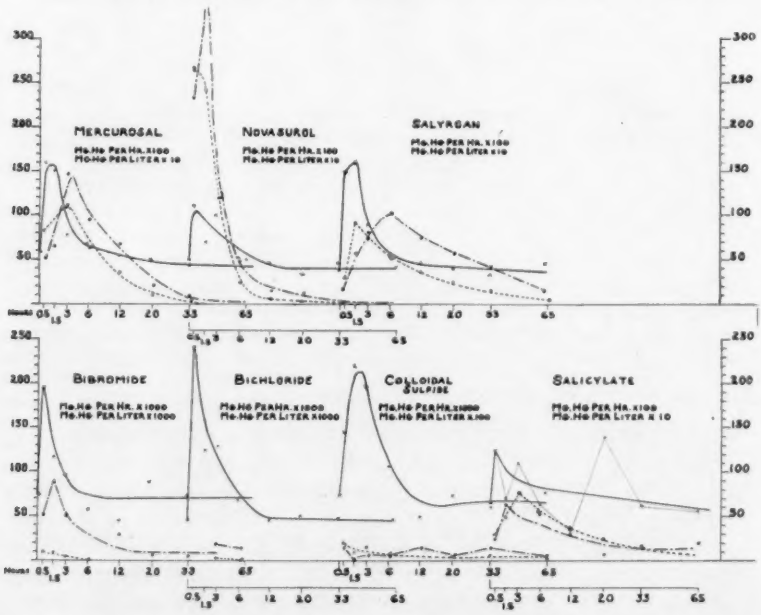

Chart 2.—Curves of means for output of urine and mercury after the clinical injection of various compounds of mercury intramuscularly.

izable inorganic compounds and flumerin. The colloidal suspensions injected intravenously and the salicylate in oil injected intramuscularly rank distinctly lower in magnitude of diuretic effect.

The most informative and significant events appear to be the total surplus excretion of urine, the maximal or peak excretion of urine, the rapidity of action when the peak is attained and the duration of action, represented by the slope of the degradation curve. These have been studied in relation to the urinary volume and to the dose, excretion and concentration of mercury.

The Total Surplus and the Peak Excretion of Urine.—These may be conveniently presented together, as they generally, if not always, tend in the same direction. The total surplus excretion of urine expresses the total amount of surplus urine (i. e., beyond the normal) excreted before the flow has returned to the normal level. The normal level was taken as the mean of the hourly output in the fore-periods and after-periods, for calculation of which were used the means obtained on the day before the injection and from eight to sixteen hours after the injection. The duration of the diuresis extends to the time when the urinary flow returns to the normal level, which may be read from charts 1 and 2. Multiplication of this time by the normal hourly urinary level gives what would be the normal volume of urine in the diuretic period, and subtraction of this normal volume from the observed volume gives the total surplus volume, in cubic centimeters, which may then be expressed as a percentage of the normal volume. These data are shown in table 1 *A*. This also gives the percentage reduced to the unit dose of mercury and of the excretion of mercury, which will be explained later.

The Maximal or Peak Excretion of Urine.—The maximal or peak excretion of urine is the hourly urinary volume at the time of maximal diuresis. Like the total excretion of urine, it may be expressed as the actual rate and as the surplus rate, the latter in cubic centimeters and in percentage of the normal rate; and these again may be expressed as "crude surplus" and with reference to the dose and excretion of mercury. It is shown in table 1 *B*, which follows the same arrangement as table 1 *A* for total excretion of urine, and in which the columns are numbered to correspond with those in table 1 *A*. Although the intensity of the diuresis is so much greater in the peak period than in the total time of diuresis (column 6), the clinical benefits depend more on the total volume than on the volume of the peak. As shown in column 10, the amount of surplus fluid in the entire period of diuresis is from 1.3 to 8 times, averaging somewhat over 3 times, that removed in the peak hour.

Surplus Excretion of Urine, Irrespective of the Ratio of Mercury.—For convenience in starting the analysis, the drugs may be combined into groups. For the total excretion of urine, expressed in percentage of the normal, the groups have the following sequence, in descending order:

Compound	Route	Percentage
Organic	Intravenous	78 to 122
Organic	Intramuscular	35 to 77
Colloidal	Intramuscular	62
Ionizable	Intravenous and intramuscular	35 to 46
Flumerin	Intravenous	23 to 28
Salicylate	Intramuscular	
Colloidal	Intravenous	3.6 to 20

TABLE 1.—*General Tabulation of the Median Values*

A. Total Excretion of Urine *

Column	1	2	3	4	5	6	7	8	9
Drugs	Single Dose, As Mercury, Mg.	Duration of Surplus Excretion, Hr.	Total Urinary Volume in This Time, Cc.	Normal Urinary Volume in This Time, Cc.	Surplus Urinary Volume in This Time, Cc.	Surplus, Percentage of Normal	Surplus, Percentage of Volume per Mg. of Mercury Administered	Mercury Excreted During Period of Diuresis, Mg.	Surplus Percentage per Mg. of Mercury Excreted in Period of Diuresis
Intravenous:									
Mercurosal	43.0	23	1,922	1,081	841	78.0	1.81	13.100	5.97
Novasurol	30.0	11	855	385	470	122.0	4.07	11.270	10.82
Salyrgan	35.0	17	1,224	680	544	80.0	2.29	20.370	3.92
Oxycyanide	8.5	16	1,107	768	339	44.0	5.11	0.320	137.00
Colloidal metal	100	20	862	720	142	20.0	0.20	0.140	143.00
Colloidal sulfide	170	8	431	416	15	3.6	0.021	0.110	32.70
Flumerin	65	16	1,006	816	190	23.0	0.35	2.110	10.90
Intramuscular:									
Mercurosal	22	20	1,352	1,000	352	35.0	1.59	9.640	3.64
Novasurol	30	12	777	564	213	38.0	1.27	8.760	4.34
Salyrgan	35	13	946	533	413	77.0	2.20	6.720	11.40
Bibromide	5.5	10	812	600	212	35.0	6.35	0.033	1,160.00
Bichloridol	..	25	1,712	1,175	537	46.0	....	0.009	5,111.00
Colloidal sulfide	50	14	1,475	910	565	62.0	1.24	0.130	477.00
Salicylate in oil	60	13	833	650	183	28.0	0.43	3.540	7.90

B. Peak of Excretion of Urine

Column	3	4	5†	6	7	8	9	10
Drug	Peak of Urinary Volume per Hour, Cc.	Normal Urinary Volume per Hour, Cc.	Surplus Peak of Urinary Volume per Hour, Cc.	Percentage of Normal Urinary Volume	Percentage per Mg. of Mercury Administered	Mercury Excreted During Peak Hour, Mg.	Peak of Urinary Volume per Mg. of Mercury Excreted in Peak Hour, Percentage	Ratio of Total Surplus Excretion to Peak Surplus Excretion
Intravenous:								
Mercurosal	180	47	133	287	6.70	3.1800	90.2	6.3
Novasurol	195	35	160	458	15.20	6.8500	68.8	3.0
Salyrgan	175	40	135	337	9.60	13.2000	28.1	4.0
Oxycyanide	175	48	127	265	30.60	0.1200	2,210.0	2.7
Colloidal metal	105	36	69	192	1.90	0.0300	6,333.0	2.1
Colloidal sulfide	83	52	31	60	0.35	0.0250	2,400.0	‡
Flumerin	200	51	149	296	4.50	0.4300	682.0	1.3
Intramuscular:								
Mercurosal	160	50	110	220	10.00	1.1100	197.0	3.2
Novasurol	115	47	68	145	4.80	2.6600	54.5	3.1
Salyrgan	160	41	119	291	8.30	0.9200	316.0	3.5
Bibromide	195	60	135	225	41.20	0.0050	46,250.0	4.4
Bichloridol	240	47	193	410	.....	0.0025	160,000.0	2.8
Colloidal sulfide	225	65	160	246	4.92	0.0200	12,300.0	3.5
Salicylate in oil	125	50	75	150	2.50	0.4800	31.2	8.2

* The columns in parts A and B are numbered uniformly for analogous values.

† The calculation of values is as follows: the value in column 5 equals that in column 3 minus that in column 4; the value in column 6 equals that in column 5 divided by that in column 4 and multiplied by 100; the value in column 7 equals that in column 6 divided by that in column 1; the value in column 9 equals that in column 6 divided by that in column 8, and the value in column 10 equals that in column 5, part A, divided by that in column 5, part B.

‡ The total diuresis was so slight that the quotient would not be significant.

The peak excretion is more uniform, so that the groups overlap and the sequence is somewhat confused, but broadly the compounds may be grouped as follows:

Compound	Route	Percentage
Organic Ionizable	Intravenous Intramuscular	225 to 458
Flumerin Ionizable Colloidal	Intravenous Intravenous Intramuscular	246 to 293
Organic Salicylate in oil	Intramuscular Intramuscular	145 to 291
Colloidal	Intravenous	60 to 192

In both the total and the peak excretion of urine the organic compounds administered intravenously stand highest, and the colloidal compounds administered intravenously, lowest. The results obtained with the others appear too much intermingled to invite generalization.

TABLE 2.—*Ranking of the Individual Compounds on the Basis of the Surplus Excretion of Urine* *

Rank	For Therapeutic Dose			For Equal Dose of Mercury			For Equal Excretion of Mercury		
A. Total Surplus Excretion									
1	Novasurol	V†	3.20	Bibromide	M	5.200	Bichloridol	M	1,173.00
2	Salyrgan	V	2.10	Oxycyanide	V	4.000	Bibromide	M	367.00
3	Mercurosal	V	2.05	Merbaphen	V	3.200	Sulfide	M	110.00
4	Salyrgan	M	2.00	Salyrgan	V	1.800	Colloidal metal.	V	33.00
5	Sulfide	V	1.63	Salyrgan	M	1.700	Oxycyanide	V	31.00
6	Bichloridol	M	1.21	Mercurosal	V	1.400	Sulfide	V	7.50
7	Oxycyanide	V	1.16	Mercurosal	M	1.250	Salyrgan	M	2.60
8	Sulfide	M	1.05	Novasurol	M	1.000	Flumerin	V	2.50
9	Novasurol	M	1.00	Sulfide	M	0.980	Novasurol	V	2.50
10	Bibromide	M	0.92	Salicylate	M	0.340	Salicylate	M	1.84
11	Mercurosal	M	0.92	Flumerin	V	0.280	Mercurosal	V	1.37
12	Salicylate	M	0.74	Colloidal metal.	V	0.160	Novasurol	M	1.00
13	Flumerin	V	0.61	Sulfide	V	0.017	Salyrgan	V	0.90
14	Colloidal metal.	V	0.52				Mercurosal	M	0.84
B. Peak Surplus Excretion									
1	Merbaphen	V	3.20	Bibromide	M	8.60	Bichloridol	M	2,940.00
2	Bichloridol	M	2.80	Oxycyanide	V	6.50	Bibromide	M	852.00
3	Salyrgan	V	2.30	Merbaphen	V	3.20	Colloidal sulfide	M	226.00
4	Mercurosal	V	2.00	Mercurosal	M	2.10	Colloidal metal.	V	116.00
5	Flumerin	V	2.00	Salyrgan	V	2.00	Salyrgan	M	58.00
6	Salyrgan	M	2.00	Salyrgan	M	1.70	Colloidal sulfide	V	44.00
7	Oxycyanide	V	1.80	Mercurosal	V	1.40	Oxycyanide	V	41.00
8	Colloidal sulfide	M	1.70	Colloidal sulfide	M	1.08	Flumerin	V	13.80
9	Bibromide	M	1.55	Merbaphen	M	1.00	Mercurosal	M	3.62
10	Mercurosal	M	1.50	Flumerin	V	0.94	Mercurosal	V	1.66
11	Colloidal metal.	V	1.30	Salicylate in oil.	M	0.52	Merbaphen	V	1.26
12	Salicylate in oil.	M	1.03	Colloidal metal.	V	0.40	Merbaphen	M	1.00
13	Novasurol	M	1.00	Colloidal sulfide	V	0.07	Salicylate in oil.	M	0.57
14	Colloidal sulfide	V	0.41				Salyrgan	V	0.52

* The compounds are arranged in each column in descending order of magnitude of potency. The quantities are expressed in multiples of values obtained with novasurol administered intramuscularly (as percentage of normal excretion of urine).

† V indicates intravenous and M intramuscular injection.

For comparison of the individual preparations it is convenient to use the results obtained with some familiar compound as a measure and to express the potency as multiples or fractions of this unit. The

mean values for novasurol injected intramuscularly were chosen for this purpose, but the conclusions would, of course, be the same if any other preparation were used as the basis for comparison. The sequence of the compounds, in descending order, and the values in this scale are shown in column 1 of table 2 for the therapeutic doses and in columns 2 and 3 for equal doses and equal excretion of mercury. With the therapeutic doses it may be remarked that novasurol administered intravenously, which heads the list, was 3 times as potent as the same preparation administered intramuscularly for both total and peak excretion of urine and that salyrgan was about twice as potent, both intravenously and intramuscularly, as novasurol injected intramuscularly by either criterion. The sequence of the three individual organic compounds is not the same for intravenous and for intramuscular injection: When given intravenously, novasurol was 1.5 times as potent as salyrgan; when administered intramuscularly, salyrgan was twice as potent as novasurol. Mercurosal ranks lowest for both routes, although not by a great distance. All the inorganic ionizable compounds induced an output of urine equal to or greater than that caused by novasurol injected intramuscularly. These statements apply equally to the total and to the peak excretion of urine, the figures for which agree closely (within one rank) for nine of the fourteen compounds. Colloidal mercuric sulfide injected intravenously and novasurol administered intramuscularly were ranked distinctly higher on the basis of the total excretion of urine, and bichloridol administered intramuscularly and flumerin and colloidal mercury injected intravenously were ranked higher on the basis of peak excretion. No generalization can be drawn from these exceptional shifts, as they may have been accidental. The general agreement of the sequence of total and peak excretion of urine is the significant feature of the comparison.

Surplus Excretion of Urine Referred to Unit Dose of Mercury.—The unit dose of mercury is shown in column 7 of table 1. For the total excretion of urine, the descending order of the compounds becomes:

Compound	Route	Percentage
Ionizable	Intravenous and intramuscular	5.1 and 6.4
Organic	Intravenous	1.8 to 4.1
Organic	Intramuscular	1.8 to 2.2
Colloidal	Intramuscular	1.24
Flumerin	Intravenous	0.35 and 0.43
Salicylate	Intramuscular	
Colloidal	Intravenous	0.02 and 0.2

This discloses an important shift in the rank of the inorganic compounds, which seem to be much more potent than the organic in a unit dose. Otherwise, the sequence remains the same. The groups are more widely separated, and the extremes do not overlap.

For the peak secretion of urine the descending order of potency of the compounds in unit doses is the same as for the total excretion, with the following values:

Compound	Route	Percentage
Ionizable	Intravenous and intramuscular	31 and 41
Organic	Intravenous	7 to 15
Organic	Intramuscular	5 to 10
Flumerin Colloidal	Intravenous Intramuscular	4.5 and 4.9
Salicylate	Intramuscular	2.5
Colloidal	Intravenous	0.35 to 1.9

The sequence of the individual compounds on the basis of their potency in comparison with the potency of novasurol administered intramuscularly is shown in column 2 of table 2. The total excretion of urine produced by the inorganic compounds is 4 or 5 times that of novasurol administered intramuscularly with an equal dose of mercury. When injected intravenously novasurol is about 3 times, salyrgan 2 times and mercurosal 1½ times as potent as novasurol administered intramuscularly. For salyrgan and mercurosal the potency by intramuscular injection is very close to that by intravenous injection, in contrast to the widespread potency of novasurol. For the colloidal compounds the potency by intramuscular injection (0.98 times) is far greater than that by intravenous injection (0.017 and 0.16 times).

The peak excretion of urine shows the same sequence, the only shift of more than one position being for mercurosal administered intramuscularly, which has a higher position for the peak than the total excretion. The superior potency of the inorganic compounds is even more apparent in the figures for the peak (6.5 and 8.6 times that for novasurol administered intramuscularly) than in those for total excretion (4 and 5.2 times that for novasurol administered intramuscularly).

Surplus Excretion of Urine Referred to Unit Excretion of Mercury.—This appears the most logical measure of potency, since it may be presumed to reflect the concentration of mercury in the blood with more certainty than does the dose, for the latter may be offset by differences in absorption and in the rate at which the compound leaves the blood stream. To establish this relation the total surplus excretion of urine was divided by the amount of mercury that had been excreted in the urine before the urinary flow had returned to the normal level, and, similarly, the amount of urine excreted at the peak of diuresis was divided by the amount of mercury excreted in the peak hour (table 1, column

9). The sequence of the group of compounds for surplus total excretion of urine is as follows:

Compound	Route	Percentage
Ionizable	Intramuscular	1,160 to 5,111
Colloidal	Intramuscular	477
Ionizable	Intravenous	137
Colloidal	Intravenous	33 and 143
Flumerin	Intravenous	11
Salicylate	Intramuscular	8
Organic	Intramuscular	3.6 to 11.4
Organic	Intravenous	3.9 to 10.8

For surplus peak excretion of urine the sequence is:

Compound	Route	Percentage
Ionizable	Intramuscular	46,250 to 160,000
Colloidal	Intramuscular	12,300
Colloidal	Intravenous	2,400 to 6,333
Ionizable	Intravenous	2,210
Flumerin	Intravenous	682
Organic	Intramuscular	55 to 316
Organic	Intravenous	28 to 90
Salicylate in oil	Intramuscular	31

The most striking feature of both sequences is the enormous superiority of the potency of the ionizable solutions to that of the organic compounds, the total excretion of urine being from 12 to 1,500 times greater and the peak excretion from 7 to 6,000 times greater. The colloidal compounds also are revealed as much more potent than the organic compounds, being from 3 to 130 times as potent for the total excretion of urine and from 8 to 440 times as potent for peak surplus excretions. In brief, on the basis of excreted mercury the organic compounds are so far inferior to the others as to justify the assumption that the diuresis caused by organic mercury is due to the liberation of small quantities of ionic mercury and that the molecule of organic mercury as such is very little, if at all, diuretic. Through this assumption, which is shared by Fourneau and Melville,[1] all diuresis caused by mercury would be reduced to a common basis.

In column 3 of table 2 is shown the sequence of the compounds in descending order on the basis of their potency in terms of novasurol administered intramuscularly. Mercury bichloride in oil administered intramuscularly ranks highest, both for total excretion of urine (1,170) and for peak excretion (2,940); next comes the bibromide administered intramuscularly (267 and 852) and third, the colloidal sulfide administered intramuscularly (110 and 226). The colloidal suspensions injected intravenously are 7.5 and 33 times as potent for total excretion of urine as novasurol administered intramuscularly and 44 and 116 times as potent for peak surplus excretion. For all these the superiority is greater for the peak than for the total excretion of urine, and the contrasts are much greater on the basis of excretion of mercury than on that of the dose of mercury. Among the organic compounds the spread is relatively small, for the total surplus excretion of urine the

spread being between 2.6 for salyrgan administered intramuscularly and 0.84 for mercurosal administered intramuscularly; for the peak excretion salyrgan administered intramuscularly stands out with 58; the next highest is mercurosal, 3.62, administered intramuscularly, with salyrgan, 0.52, administered intravenously. Salyrgan administered intramuscularly stands highest throughout, but the others intermingle without apparent order as to the compounds and the route of injection.

In a comparison of the ranking of dosage and excretion of mercury (by the positions in table 2) the bromide holds first or second place throughout, but most of the other compounds shift markedly and significantly, being essentially alike for total and peak excretion of urine.

TABLE 3.—*Comparison of Surplus Excretion of Urine Following Intravenous and Following Intramuscular Injection of Various Compounds* *

	Therapeutic Dose	Equal Dose of Mercury	Equal Excretion of Mercury
	1	2	3
A. Total Surplus Excretion			
Mercurosal	78/35 = 2.2	1.81/1.50 = 1.14	5.97/3.64 = 1.63
Novasurol	122/38 = 3.2	4.07/1.27 = 3.2	10.8/4.34 = 2.5
Salyrgan	80/77 = 1.04	2.29/2.20 = 1.04	3.92/11.4 = 0.34
Oxycyanide and bibromide	44/35 = 1.25	5.11/6.35 = 0.80	137/1,160 = 0.12
Colloidal sulfide	3.6/62 = 0.06	0.021/1.24 = 0.017	32.7/477 = 0.069
B. Peak Surplus Excretion			
Mercurosal	287/220 = 1.3	6.7/10.0 = 0.67	90.2/197 = 0.47
Novasurol	458/145 = 3.4	15.2/4.8 = 3.2	68.8/54.5 = 1.3
Salyrgan	337/291 = 1.12	9.6/8.3 = 1.2	28.1/316 = 0.09
Oxycyanide and bibromide	265/225 = 1.2	30.6/41.2 = 0.74	2,210/46,250 = 0.05
Colloidal sulfide	60/160 = 0.37	0.35/4.92 = 0.07	2,400/12,300 = 0.195

* The percentage of surplus excretion is based on the formula: value for intravenous injection divided by value for intramuscular injection equals quotient.

The changes may be summed up thus, that the organic compounds have a relatively higher potency on the basis of dosage and the colloidal suspensions (including flumerin) have a higher potency on the basis of excretion. This is equivalent to saying that the mercury of the organic compounds is less diuretic than that of the colloidal compounds; and this again is merely saying that the organic mercury as such is, at least relatively, inactive. Colloidal mercury is presumably equally inactive, but it does not circulate long in this form, nor is it excreted in this form.

Comparison of the Diuretic Potency of Intravenous and Intramuscular Injections.—A priori, it would probably be assumed that compounds should have greater potency when injected intravenously, especially for the peak excretion of urine. Analysis of the data shows that this assumption would generally be wrong. In table 3 the relative

diuretic potency of intravenous and intramuscular injections is shown as the quotient $\frac{V}{M}$. Column 1, in which the dose is not taken into account, has little significance. Column 2, showing the results for equal doses of mercury is the most important practically. The columns show that only novasurol has a materially higher potency when injected by vein than when injected by muscle, with a quotient of 3.2 for both total and peak surplus excretion of urine. The quotients for mercurosal and salyrgan range between 1.2 and 0.67 for peak excretion and nearer 1 for total excretion, probably within the range of accidental variation. For the inorganic compounds the potency on intramuscular injection somewhat surpasses that on intravenous injection, with $\frac{M}{V}$ equaling 1.25, for total excretion of urine and 1.33 for peak excretion. With the colloidal sulfide, the superiority of the intramuscular over the intravenous route is marked, with $\frac{M}{V}$ equaling 60 for total and 14 for peak excretion of urine. This may be due to rapid flocculation of the solution when injected intravenously, which would make it relatively ineffective.

On the basis of the amount of mercury excreted (column 3 of table 3), novasurol is again distinctly more effective when injected intravenously, with $\frac{V}{M}$ equaling 2.5 for total and 1.3 for peak excretion of urine. The superiority is therefore not as marked as on the basis of the equal doses. The potency of mercurosal is irregular, with the intravenous route superior ($\frac{V}{M}$ equaling 1.63) for total excretion of urine and inferior (0.47) for peak excretion. In the case of salyrgan the intramuscular route is markedly more effective, with $\frac{M}{V}$ equaling 3 for total and 11 for peak excretion of urine. For the inorganic compounds the superiority of the intramuscular route also becomes more marked, with $\frac{M}{V}$ equaling 8 for total and 20 for peak excretion; for colloidal sulfide the superiority of the intramuscular route persists but is less marked, $\frac{M}{V}$ equaling 15 for total and 5 for peak excretion.

In a review of all the data on the comparison of the potencies of compounds administered by the intravenous and intramuscular routes, it is notable that the potency of a compound when given intravenously is inferior to that of the compound when given intramuscularly more often than it is superior (in the four columns of table 3, the potency on intravenous administration is greater 8 times and the potency on intramuscular administration 12 times). Only novasurol was consistently superior in potency on intravenous injection. The superiority of intramuscular injection was most marked for the injections of the colloidal compounds, presumably because when injected intravenously these compounds rapidly become inactive owing to flocculation. For the

inorganic ionizable and for the organic compounds the superiority of intramuscular injections is generally markedly greater on the basis of equal excretion of mercury than on that of equal doses of mercury; and somewhat greater for peak than for total surplus excretion of urine.

Speed and Duration of the Diuretic Action, or the Slope of the Degradation Curve.—Tabulations were made of the hour when the diuresis and the output and concentration of mercury reached their peak and of the number of hours between these peak values and the times when the surplus excretion of urine, the output of mercury per hour and the concentration of mercury had returned by one-third, one-half, two-thirds and entirely to the normal level.

The means for all the observations on all the compounds form a convenient point of departure. They are given in table 4 and figure 3. This shows graphically that the speed and duration of the three factors

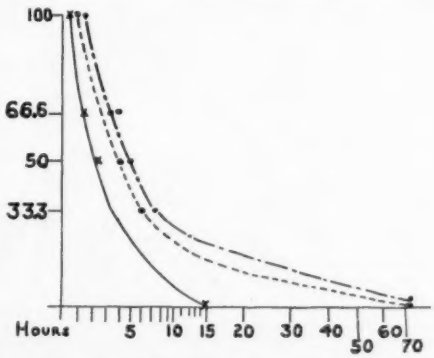

Chart 3.—Curves of degradation of surplus excretion of urine and of excretion of mercury from peak to zero, with means of all the observations on all the compounds.

—surplus excretion of urine, the amount of mercury and the concentration of mercury—run closely parallel. The two curves for mercury are almost identical, and that for urinary output differs only in that the curve is degraded almost twice as rapidly.

Comparison of the individual compounds in table 5 shows the mean time of the peak and of the half-degradation and return to normal. The one-third and two-thirds degradation times also were tabulated and compared but are not reproduced, since the half-degradation adequately represents the whole sequence of degradation, and is least subject to accidental distortion. The concentration of mercury is shown but will not be discussed, since the concentration of mercury in the blood stream would be reflected more consistently in the amount of mercury excreted at the given moment than by its concentration in the urine.

As the peak is generally attained within one or two hours, the unit of hour periods permits only a coarse classification. The peak of urinary volume was attained within an hour by twelve of the fourteen methods of administration of seven compounds intravenously and of seven intramuscularly. Of these, with seven there had already been a material decline in the second hour and with five in the third hour. With only

TABLE 4.—*General Means of the Peaks of Excretion and Degradation Times*

	Surplus Excretion	Mercury per Hour, Mg.	Mercury per Liter, Mg.
Hours to peak	< 1 hour	1.0	1-2
Hours from peak to one-third return	1.5	3.7	3.4
Hours from peak to one-half return	2.1	4.0	4.4
Hours from peak to two-thirds return	3.1	6.3	7.2
Hours from peak to normal	15.0	72.0	72.0

TABLE 5.—*Means for Individual Compounds for Peaks of Excretion and Degradation Times*

	Surplus Excretion			Urinary Excretion of Mercury per Hour			Urinary Mercury per Liter		Peak Levels		
Drug	Injection to Peak, Hr.	Peak to Half Level, Hr.	Peak to Normal, Hr.	Injection to Peak, Hr.	Peak to Half Level, Hr.	Peak to Normal, Hr.	Injection to Peak, Hr.	Peak to Half Level, Hr.	Surplus Excretion, Cc. per Hr.	Mercury, Mg. per Hr.	Mercury, Mg. per Liter
Intravenous:											
Mercurosal	1 to 2	4.9	23	0 to 1	3.70	..	0 to 1	4.20	133	3.1800	19.50
Novasurol	0 to 2	2.7	11	0 to 1	1.75	72	0 to 1	1.75	160	6.8500	38.10
Salyrgan	0 to 2	2.6	17	0 to 1	1.70	72	0 to 1	1.70	135	13.2000	75.40
Oxycyanide	0 to 2	2.0	16	0 to 1	2.00	16	0 to 1	2.00	127	0.1200	0.69
Colloidal mercury	0 to 1	1.7	20	0 to 1	3.00	8	0 to 2	11.40	69	0.0300	0.28
Colloidal sulfide	0 to 1	1.5	8	0 to 2	5.20	24	0 to 4	9.30	81	0.0250	0.31
Flumerin	0 to 1	1.0	16	1 to 2	4.00	132	1 to 2	4.80	149	0.4300	6.30
Intramuscular:											
Mercurosal	0 to 2	1.9	20	2 to 4	9.70	108	2 to 4	11.70	110	1.1100	14.80
Novasurol	0 to 1	2.2	12	0 to 2	3.30	108	1 to 2	3.50	68	2.6600	35.10
Salyrgan	0 to 2	2.7	13	1 to 2	11.80	108	4 to 8	33.10	119	0.9200	10.20
Bibromide	0 to 1	1.3	10	0 to 2	4.00	24	1 to 2	4.40	135	0.0050	0.09
Bichloridol	0 to 1	2.0	25	2 to 4	7.60	..	2 to 4	10.80	193	0.0025	0.02
Colloidal sulfide	2 to 3	3.8	14	0 to 1	5.00	..	0 to 1	1.70	160	0.0150	0.14
Salicylate in oil	0 to 1	3.0	13	1 to 2	11.30	144	1 to 2	....	75	0.4800	6.85

two was more than an hour required to attain the peak of urinary volume; viz., with mercurosal injected intravenously the peak was reached between one and two hours, and with colloidal sulfide administered intramuscularly, in from two to three hours. The distribution of the other peaks does not show any apparent orderly relation as to compounds or route of injection.

The attainment of the peak of excretion of mercury per hour, on the other hand, is distinctly faster after intravenous than after intramuscular injection; with six of the seven compounds injected intra-

venously and with only three of the seven compounds injected intramuscularly, the peak was reached within an hour, and with none of those injected intravenously but with two of those injected intramuscularly, viz., mercurosal and bichloridol, more than two hours was required. The distribution of the individual compounds does not show any apparent orderly relation.

Correlation of Time of Attainment of Peak and Degradation.—This is shown by the following means of time (the figures in parentheses show the number of compounds represented in each quantity):

To Peak, Hours	Half-Degradation Surplus Excretion of Urine, Hours	Mercury Excreted per Hour, Hours
0-1	1.8 (7)	2.8 (6)
0-2	2.4 (5)	4.2 (3)
1-3	4.4 (2)	.....
2-4	.....	8.9 (5)

The correlation is significant for both diuresis and excretion of mercury. It is explained by the assumption that slower absorption or mobilization of active mercury means that a longer time is required to reach a peak and that the mercury continues to be active longer after the peak has been passed.

Comparison of Peak Level and Half-Degradation Time.—When the data for each class are arranged in the order of height of peak, there is no concordance in any of the factors (urinary volume, amount and concentration of mercury) between the height of the peak and the time of degradation. It may therefore be considered as definitely settled that the height of the peak has essentially no influence on the rate of degradation. This dispenses with the need of considering dosage in the further treatment of the data.

Group Study of Half-Degradation Time.—This is shown in table 6, which indicates the following generalizations: There is little, if any, difference between the mean values for intravenous and those for intramuscular injections as regards the duration of diuresis, but the excretion of mercury is markedly more prolonged with intramuscular injections. This prolonged excretion of mercury holds true for the intramuscular injection of both the organic and the ionizable inorganic compounds, but the associated diuresis appears distinctly shorter, especially that for the organic compounds. The colloidal suspensions show the reverse effect. The period of diuresis following intramuscular injection is markedly longer than that following intravenous injection, and the difference in the excretion of mercury is relatively small.

The inorganic ionizable compounds produce a briefer duration both of diuresis and of excretion of mercury than do the organic compounds, by either route.

The colloidal compounds injected intravenously cause the shortest period of diuresis of all the compounds, except flumerin, and the longest period of excretion of mercury of all the compounds injected intravenously.

The colloidal suspensions injected intramuscularly cause the longest period of diuresis of all the compounds and the shortest period of excretion of mercury of all the compounds injected intramuscularly.

TABLE 6.—*Mean of Half-Degradation Time by Groups in Hours from the Peak*

Compounds	Surplus Excretion	Mercury, Mg. per Hour	Mercury, Mg. per Liter
All	1 to 4.9	1.7 to 11.8	1.7 to 33.1
Mean	2.1	4	4.4
All (intravenous injections)	1 to 4.9	1.7 to 5.2	1.7 to 11.4
Mean	2.0	2.9	3.7
All (intramuscular injections)	1.3 to 3.9	3.3 to 11.8	1.7 to 33.1
Mean	2.3	7.4	7.6
Organic (intravenous injections)	2.2 to 4.9	1.7 to 3.7	1.7 to 4.2
Mean	3.2	2.4	2.6
Organic (intramuscular injections)	1.9 to 2.7	3.3 to 11.8	3.5 to 33.1
Mean	2.3	8.3	16.1
Inorganic (intravenous injections)	2.0	2.0	2.0
Inorganic (intramuscular injections)	1.3 to 2.0	4.0 to 7.6	4.4 to 10.8
Mean	1.7	5.8	7.6
Colloidal (intravenous injections)	1.5 to 1.7	3.0 to 5.2	9.3 to 11.4
Mean	1.6	4.1	10.4
Colloidal (intramuscular injections)	3.9	5.0	1.7
Flumerin	1.0	4.0	4.8
Salicylate in oil (intramuscular injections)	3.0	11.3	...

TABLE 7.—*Ranking of Compounds According to Half-Degradation Time in Ascending Order*

Rank	Surplus Excretion		Hours	Mercury per Hour		Hours	Mercury per Liter		Hours
1	Flumerin	V	1.0	Salyrgan	V	1.70	Salyrgan	V	1.70
2	Bibromide	M	1.3	Novasurol	V	1.75	Colloidal sulfide	M	1.70
3	Colloidal sulfide	V	1.5	Oxycyanide	V	2.00	Novasurol	V	1.75
4	Colloidal metal	V	1.7	Colloidal metal	V	3.00	Oxycyanide	V	2.00
5	Mercurosal	M	1.9	Novasurol	M	3.20	Novasurol	M	3.50
6	Bichloridol	M	2.0	Mercurosal	V	3.70	Mercurosal	V	4.20
7	Oxycyanide	V	2.0	Flumerin	V	4.00	Bibromide	M	4.40
8	Novasurol	V	2.2	Bibromide	M	4.00	Flumerin	V	4.80
9	Novasurol	M	2.2	Colloidal sulfide	M	5.00	Colloidal sulfide	V	9.80
10	Salyrgan	V	2.6	Colloidal sulfide	V	5.20	Bichloridol	M	10.80
11	Salyrgan	M	2.7	Bichloridol	M	7.60	Colloidal metal	V	11.40
12	Salicylate in oil	M	3.0	Mercurosal	M	9.70	Mercurosal	M	11.70
13	Colloidal sulfide	M	3.9	Salicylate in oil	M	11.30	Salyrgan	M	33.10
14	Mercurosal	V	4.9	Salyrgan	M	11.80	Salicylate	M	.....

The ranking of the individual compounds by half-degradation time from quickest to slowest is shown in table 7. The following particulars may be added to the generalization of the group rankings:

For surplus excretion of urine practically all the organic compounds give results somewhat below the mean value. The values for intramuscular and intravenous injections rank close together, except for those

for mercurosal, with which the diuresis following intravenous injections lasts over 2.5 times that following intramuscular injection. The values for colloidal suspensions injected intravenously, including flumerin, show diuresis of short duration, while the period of diuresis following the intramuscular injection of colloidal mercuric sulfide is one of the most prolonged. The action of mercuric salicylate also is slow.

For the excretion of mercury (per hour) the most striking feature is the shorter duration following the intravenous injection, which has been discussed. The distribution of the individual compounds according to rank appears to be irregular, with little relation to their ranking for diuresis; twelve of the fourteen compounds differ by more than one rank, indicating that some feature other than the gross circulation of mercury is concerned in the diuresis, presumably ionization. It is curious that the period of diuresis after the intravenous injection of salyrgan ranks with the shortest and that after the intramuscular injection of this compound, with the longest.

TABLE 8.—*A Comparison of the Half-Degradation Time of the Compounds After Intravenous and After Intramuscular Injection* *

	Surplus Excretion	Mercury per Hour
Mercurosal	4.9/1.9 = 2.6	3.7/9.7 = 0.38
Novasurol	2.7/2.2 = 1.2	1.75/3.3 = 0.53
Salyrgan	2.6/2.7 = 0.96	1.7/11.8 = 0.14
Oxycyanide and bibromide	2.0/1.3 = 1.5	2.0/4.0 = 0.50
Colloidal sulfide	1.5/3.8 = 0.40	5.2/5.0 = 1.04

* The figures are based on the formula: values for intravenous injections divided by values for intramuscular injection equals quotient.

The relative duration (half-degradation) of the diuresis and of the excretion of mercury produced by intravenous and intramuscular injection of the individual compounds is shown as quotients in table 8.

SUMMARY AND CONCLUSIONS

A series of organic, inorganic and colloidal compounds of mercury injected intramuscularly and intravenously in clinical practice were compared as to diuretic response. Observations on the peak of excretion of urine and the total surplus output of fluid were found to lead to the same general conclusions:

The organic compounds cause somewhat greater diuresis in therapeutic doses; but with reference to the dose of mercury, and especially to the amount of mercury excreted, the organic compounds are far surpassed both by ionizable inorganic and by colloidal compounds. The superiority of the ionizable compounds is so marked that it suggests that the diuretic action of all mercurial compounds may be due to the liberation of some mercury ions.

Reactions to intramuscular and those to intravenous injections do not differ consistently in degree, speed or duration of diuresis, although the excretion of mercury is more rapid following intravenous injections.

Practically all the curves for urinary output and excretion of mercury have a similar form, except that the curve for urinary output declines about twice as rapidly as that for the excretion of mercury.

The rapidity of ascent and descent of the curves for both urinary output and excretion of mercury tends to vary in the same direction, but the height of the maximal level of urinary output or of excretion of mercury has no consistent effect on the duration.

The organic compounds cause somewhat more prolonged periods of diuresis and excretion of mercury than the inorganic compounds, injected both by vein and by muscle. The colloidal compounds cause the shortest period of diuresis when injected by vein and the longest period of excretion of mercury when injected by muscle. They cause the longest period of diuresis and the shortest period of excretion of mercury.

The differences among the compounds of each group are minor and do not suggest a significant generalization.

UNTOWARD EFFECTS OF DIURESIS

WITH SPECIAL REFERENCE TO MERCURIAL DIURETICS

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The syndrome to be discussed in this paper is seen in connection with diuresis and is characterized by preliminary symptoms of weakness, restlessness and mental confusion (sometimes progressing to delirium and psychosis), which may be followed by apathy, coma and in some cases death. The turgor of the tissues may become poor, the tongue exceedingly dry and thirst extreme. In some instances the premonitory symptoms of restlessness and confusion do not appear, the syndrome being ushered in by apathy. Simple though profound weakness often follows marked diuresis, and when it occurs alone, it is not to be considered as an alarming or serious symptom. It is the mildest expression of this clinical picture but is not significant because the organism automatically reestablishes its equilibrium after a longer or shorter time. Any or all of these phenomena may appear concomitantly with complications inherent in the underlying disease process or in association with other superimposed complications. However, they are often distinguishable even in the face of these confusing factors and, in any event, should be borne in mind when a patient who has been subjected to diuretic therapy appears to be failing.

There is nothing new in this syndrome as described. Eichhorst [1] in 1898 was able with digitalis and theobromine sodiosalicylate to produced marked diuresis, after which somnolence, disorientation, delirium and apathy developed in certain cases. Sprague and Graybiel [2] mentioned a case of malignancy with ascites in which they thought that death was hastened by the marked effect of salyrgan. Srnetz [3] in 1934 stressed the necessity for care in administering salyrgan to patients

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1. Eichhorst, H.: Toxämische Delirien bei Herzkranken, Deutsche med. Wchnschr. **24**:389 (June 23) 1898.

2. Sprague, H. B., and Graybiel, A.: Salyrgan as a Diuretic: Report of Sixty Cases, New England J. Med. **204**:154 (Jan. 22) 1931.

3. Srnetz, K.: Vorsicht mit Salyrgan bei schwerer Herzschwäche, München. med. Wchnschr. **81**:1891 (Dec. 6) 1934.

with severe cardiac insufficiency and mentioned somnolence and mental confusion following diuresis.

It is important to emphasize that the clinical picture herein described may conceivably be produced without the use of mercurial diuretics and that in no sense are these observations to be taken as an indictment of these valuable drugs. Qualitatively, though not quantitatively, the xanthines [4] produce the same effect as the mercurials. Even in spontaneous diuresis, such as may occur when a patient with cardiac decompensation is put to bed, there is a loss not only of water but of sodium chloride as well. If the intake of salt and water is then unduly restricted, the condition which we have already described may develop, despite the fact that diuretic drugs have not been used. Other disorders involving the depletion of water and salt may present similar features.

However, the problem which is presented has assumed greater importance in the past decade, since it was during this period that the mercurial diuretics were introduced into general use. Although the symptoms we have described are not in any sense pathognomonic of a condition caused by salyrgan and allied drugs, these phenomena are so intimately bound up with their use that any discussion of the problem must necessitate a discussion of the mercurial diuretics as well. This syndrome is more likely to occur when mercurial diuretics are used, since their ability to cause rapid dehydration is more marked than that of any other available diuretic agent.

The facts which are most pertinent to the problem are as follows:

1. It has been shown that in diuresis due to salyrgan and related drugs there is a huge excretion of sodium chloride and water [5] (Cha-

4. Blumgart, H. L.; Gilligan, D. R.; Levy, R. C.; Brown, M. G., and Volk, M. C.: Action of Diuretic Drugs, Arch. Int. Med. **54**:40 (July) 1934.

5. The clinical picture already outlined calls to mind the weakness, apathy and coma seen in the acute crises of Addison's disease, which may be precipitated by deprivation of sodium (Loeb, R. F.; Atchley, D. W., and Stahl, J.: The Rôle of Sodium in Adrenal Insufficiency, J. A. M. A. **104**:2149 [June 15] 1935). It is interesting to note that the syndrome of heat cramps (Talbott, J. H.: Heat Cramps, Medicine **14**:323 [Sept.] 1935) is also associated with a diminution of the sodium content of the blood, although clinically it appears to have little in common with the acute collapse of Addison's disease and the syndrome herein described.

Blumgart has shown that sodium, potassium and calcium are excreted in the urine in the same proportion in which they occur in blood plasma and extracellular fluids; i. e., 145 milliequivalents of sodium, 4 milliequivalents of potassium and 4 milliequivalents of calcium per liter. During the period of induced diuresis he found no alterations of these constituents in the blood; chloride, however, was excreted in larger amounts than the basic ions (190 milliequivalents) and in some instances was associated with an initial period of hypochloremia. On the first day after diuresis there was almost complete retention of available sodium chloride.

banier, Lebert and Lumière;[6] Keith, Barrier and Whelan,[7] and Blumgart[4]).

2. The degree of diuresis is dependent on the amount of the mercurial administered. When the dose of merbaphen is increased from 1 to 2 cc. there is a threefold increase in the excretion of water and sodium chloride and a twofold increase in the duration of the action (Blumgart[4]).

3. The greater the diuresis, the longer the time required by the body to regain its fluid.[4]

4. The larger the subject, i. e., the greater the available amount of body fluid, the greater the diuretic response.[8]

5. To overcome the emaciation associated with diuresis in experimental animals (used for determining minimal toxic doses of mercurials) Fourneau and Melville[9] found that fluid administered by mouth was more effective than that given parenterally. This confirmed Gunsberg's previous work.[10]

In *The Journal of the American Medical Association* for Sept. 15, 1934,[11] in the section on "Queries and Minor Notes" a question is asked concerning the untoward effects after the fifth and sixth injections of salyrgan. The following quotations from the answer are pertinent.

> Mercurial diuresis is intimately associated with the available sodium chloride and during mercurial diuresis large quantities of sodium chloride are eliminated in the urine. When salyrgan is used, the sodium chloride reserves of the body often become depleted, particularly if the patient is on a low sodium chloride intake. . . . Furthermore, some authors have felt that following sodium chloride depletion in the body further doses of salyrgan may give reactions as a result of hypochloremia.

We believe that the sodium ion may prove to be an important factor in these cases, since in patients receiving ammonium chloride and cal-

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6. Chabanier, H.; Lebert, M., and Lumière, F.: Analyse physiologique de l'action du 440-B (ou neptal), Bull. Soc. franç. d'urol. **6**:259 (Dec. 19) 1927.

7. Keith, N. M.; Barrier, C. W., and Whelan, M.: The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, J. A. M. A. **85**:799 (Sept. 12) 1925.

8. Blumgart and others.[4] The presence of edema is no assurance that the patient is not suffering from salt and water deprivation. He may complain of great thirst and present poor turgor of the tissues over the upper half of the body. The mechanism of this clinical fact is a moot point.

9. Fourneau, E., and Melville, K. I.: Studies in Mercurial Chemotherapy: I. Concerning Mercurial Toxicity; Its Evaluation, Mechanism, and Relation to Chemical Constitution, J. Pharmacol. & Exper. Therap. **41**:21, 1931.

10. Gunsberg, H.: Diureseversuche, Arch. f. exper. Path. u. Pharmakol. **69**: 381, 1912.

11. Treatment of Cardiac Decompensation, Queries and Minor Notes, J. A. M. A. **103**:858 (Sept. 15) 1934.

cium chloride as adjuvants to diuresis some, if not all, of the chloride ion is replaced; yet they may also show some or all of the symptoms we have described. In fact, a state of acidosis may be produced with depression of the carbon dioxide of the blood (case 1). In any event, the sodium ion seems to be most important for the replacement and retention of water in the intercellular spaces.[12]

As has already been mentioned, when a patient who is subjected to dehydration therapy begins to fail, the explanation is often difficult in view of the underlying disease processes and complications usually found in such subjects. One must endeavor to decide whether any of the following factors are present and, if so, whether they are etiologic, contributory or only incidental to the clinical picture: (1) irremediable myocardial insufficiency, (2) fresh coronary thrombosis, (3) exacerbation of rheumatic carditis, (4) pulmonary infarction, (5) infection of the respiratory tract, (6) true renal insufficiency,[13] (7) cerebral vascular accident, (8) excessive use of sedatives and (9) the syndrome dealt with in this paper.

The eighth possibility is of great importance, as the edematous patient with myocardial insufficiency is often extremely restless and large doses of sedatives are required to induce quietude and thus spare the myocardium. The stupor induced by rapid dehydration is too readily attributed to the use of sedatives (see case 2).

A study of our case reports and of those recorded by other observers provides no entirely adequate basis for the prediction and exclusion of patients unfavorable for drastic dehydration therapy. As stated previously, the following factors should be taken into consideration, and particular care should be exercised in their presence: old age, advanced atherosclerosis[14] and cachexia. The renal function, as determined by the concentrating power of the kidneys, is important (Saxl[15]). The

12. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

13. If hypochloremia is present, the histologic picture of the kidneys may be confusing, since the kidney in a case of pyloric obstruction—another condition associated with hypochloremia—and the kidney in a case of mercurial disease present similar features, namely, tubular degeneration and calcification (Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425 [Sept.] 1923. Zeman, F. D.; Friedman, W., and Mann, L. T.: Kidney Changes in Pyloric Obstruction, Proc. Soc. Exper. Biol. & Med. **21**:179, 1923).

14. Reference should be made to the poor prognosis in patients over 45 years of age with diabetic coma, dehydration and vasomotor collapse in Lande's series (Lande, H.: Uncontrollable Causes of Death in Diabetic Coma, J. A. M. A. **101**:9 [July 1] 1933) and to case 3 of our series.

15. Saxl, P.: Letale Quecksilberintoxikation nach einmaliger Novasurol Injektion, Wien. klin. Wchnschr. **16**:437, 1925.

test dose should be small, since the diuretic response is a function of the dose (Blumgart [4]). One point of warning should be included here. If the test dose is ineffective and thoracentesis or paracentesis is then performed, a subsequent injection of the diuretic drug may produce a too dramatic and undesirable result, which is thought to be due to improvement of the cardiac action in the former instance and to improvement of the renal circulation in the latter. This should be borne in mind before one proceeds with the second injection. Furthermore, it is important to dehydrate the patient gradually, if possible; since the more rapid and drastic the dehydration, the longer and more difficult it is for the organism to regain its water and sodium chloride equilibrium.[4] Finally, one should avoid carrying out too many procedures (such as phlebotomy, thoracentesis, paracentesis abdominis and the administration of diuretic drugs) at one time. This admonition applies particularly in the case of patients of advanced age with predominating failure of the right side of the heart, ascites, pleural effusions and subcutaneous edema.

If, despite these precautions, untoward symptoms develop, therapy should be begun as soon as the syndrome we have discussed is diagnosed or suspected. It consists of the following measures:

1. The administration of water—by mouth if possible.

2. The administration of sodium chloride by mouth, at first in capsules and later as a 0.1 per cent solution, which is effective in the restoration of the sodium content of the blood.[16]

3. Parenteral administration, if the foregoing methods are impossible. The intravenous and subcutaneous methods of treatment are not as effective as the oral route.

If therapy is delayed, the condition is no longer reversible and may end fatally.

REPORT OF CASES

Case 1.—R. F., a 57 year old woman, at the time of admission to the hospital had edema of the legs and abdominal wall, dyspnea and orthopnea. The diagnosis was generalized arteriosclerosis with coronary involvement, myocardial insufficiency and hypertension. After dehydration therapy, which included the administration of ammonium chloride and neptal (an addition product of mercury acetate and salicylamino-allylacetic acid) [17] (1.5 cc. intramuscularly), she lost 32 pounds (14.5 Kg.). The carbon dioxide content of the blood, which was 58 volumes per cent when the patient was admitted to the hospital, fell to 44.5 volumes per cent. As the congestive phenomena improved, the patient showed mental confusion and restlessness, which persisted for eight days. Though there were no focal neuro-

16. Talbott, J. H.: Heat Cramps, Medicine **14**:323 (Sept.) 1935.

17. The various mercurial diuretics mentioned in these case reports were supplied in the form of approximately 10 to 13.5 per cent aqueous solutions.

logic signs and despite the fact that there were no mental changes while there was severe decompensation, the condition was attributed to cerebral arteriosclerosis plus cardiac decompensation. No further injections of mercurial diuretics were given. Although the general dehydration measures were not discontinued, the patient recovered.

Fifteen months later the patient was readmitted to the hospital because of increasing decompensation for five weeks. She received three injections of mercupurin (an addition product of theophylline and a mercurated propyl derivative of a camphoric amine) over a period of eighteen days, with resulting pronounced diuresis. She then complained of profound weakness, began to act peculiarly and refused to cooperate. Eighteen days after her readmission to the hospital she went into vasomotor collapse, the clinical picture resembling that of acute coronary thrombosis, though without electrocardiographic changes as compared with previous records. Fluids were forced, and in the next three days the patient's condition improved remarkably, so that she was discharged from the hospital in one month.

In this case restlessness, mental changes and a period of vasomotor collapse occurred during dehydration therapy. By omitting further injections of neptal during the patient's first stay in the hospital and by forcing fluids during her second stay, recovery was obtained.

Case 2.—G. M., a 65 year old man, entered the hospital complaining of dyspnea and orthopnea of four months' duration. The diagnosis was generalized arteriosclerosis with coronary involvement, auricular fibrillation, chronic bronchitis and emphysema and myocardial insufficiency. The patient was placed on a dehydration regimen, which included three injections each of 2 cc. of salyrgan, administered one day, one week and two weeks, respectively, after the patient's admission to the hospital. During the first two weeks of his hospital stay he lost 30 pounds (13.6 Kg.) in weight and complained of severe weakness and diarrhea. Four days later stomatitis and pharyngitis developed, and there was a slight rise in temperature. The patient became unresponsive and uncooperative, refusing food and fluids. The symptoms were at first ascribed to the use of chloral hydrate. However, during the following three days fluids were forced, the stomatitis and diarrhea subsided and the patient became more responsive and cooperative. He was permitted to gain several pounds, and there was no evidence of congestive failure. One month after his admission to the hospital he was able to be discharged. This is an instance of severe weakness and uncooperativeness following drastic diuresis. It is probable that the symptoms of diarrhea and stomatitis were due to mercurialism, although this feature of the case was not investigated. It should be remarked further that the untoward symptoms were at first attributed to the use of chloral hydrate, which had been exhibited only in average doses. With the administration of fluids in liberal amounts recovery ensued.

Case 3.—R. H., a 73 year old woman, entered the hospital because of dyspnea, orthopnea and edema. The diagnosis was generalized arteriosclerosis, coronary arteriosclerosis, auricular fibrillation, myocardial insufficiency with pulmonary congestion, hepatic congestion and edema of the legs. On dehydration therapy, including two injections of neptal, each of 1.5 cc., given one and four days after her admission to the hospital, the patient lost 25 pounds (11.4 Kg.) in weight. Her convalescence was interrupted by a period of drowsiness, which, in view of the evident dehydration, was attributed to the vigorous diuretic measures. When all medication except digitalis was discontinued and the intake of fluids was increased, the patient improved remarkably and did not gain any weight. She was discharged improved one month after her admission to the hospital.

In a subsequent admission eighteen months later, the patient was acutely ill but alert, talkative and cooperative. She had had symptoms of congestive failure for four weeks. Diuresis was established with mercupurin. On the following day severe weakness and drowsiness developed. These symptoms were combated with fluids administered hypodermically and intravenously. However, the general condition grew worse rapidly; the patient went into peripheral circulatory collapse, was obviously dehydrated and had a terminal temperature of 107.6 F.

During the patient's first stay in the hospital a period of drowsiness followed dehydration. During her second stay diuresis was rapidly followed by circulatory collapse and terminal hyperpyrexia.

CASE 4.—J. V., a 65 year old man, entered the hospital because of myocardial insufficiency due to disease of the coronary arteries. He was placed on dehydration therapy, which included 1 cc. of salyrgan given intravenously. Although the patient's original weight was only 94 pounds (47.2 Kg.), there was pronounced diuresis. The following day he became noisy and irrational and had delusions of persecution requiring the administration of morphine and chloral hydrate. Progressive weakness ensued, and the patient was obviously dehydrated. Fluids were forced, but he became stuporous and died with a terminal temperature of 101.4 F.

This case illustrates the point that a patient with a small body weight, i. e., with a small reserve of salt and fluid, should be dehydrated cautiously.

CASE 5.—M. K., a 65 year old woman, was admitted to the hospital with complaints of dyspnea and edema. The diagnosis was generalized arteriosclerosis, including coronary arteriosclerosis, myocardial insufficiency, hydrothorax on the right and edema of the legs. The patient was placed on dehydration therapy and received three injections of mercupurin, each of 2 cc. She lost 38 pounds (17.3 Kg.) in weight over a period of twelve days. When signs of decompensation had disappeared and the patient was ready to be out of bed, she became drowsy and uncooperative, refusing food, fluids and medication. When fluids were forced, these symptoms cleared up, and the patient was able to leave the hospital much improved one month after her admission. The same sequence of events had been observed on two previous admissions.

This case is one in which drowsiness and lack of cooperation regularly followed the period of dehydration.

CASE 6.—A. S., a 68 year old woman, was admitted to the hospital with symptoms of progressive dyspnea and orthopnea, which had been increasing for three months. The diagnosis was generalized arteriosclerosis, coronary arteriosclerosis and myocardial insufficiency with hydrothorax on the right. The patient was immediately placed on dehydration therapy, including digitalis and 2 cc. of neptal. When admitted to the hospital she was verbose but entirely rational, dyspneic and orthopneic. In three days there was a loss of 10 pounds (4.5 Kg.). On the third day, the temperature rose to 103 F., and the patient became intensely cyanotic and unresponsive. The following morning she became irrational, and soon thereafter she died. In this case the sudden change which occurred after three months of cardiac decompensation was coincidental with and probably attributable to the rapid dehydration therapy.

CASE 7.—A 67 year old man entered the hospital complaining of exertional precordial pain of ten years' duration and dyspnea and edema of four months' duration. The diagnosis was generalized arteriosclerosis, with cerebral and coronary involvement and myocardial insufficiency. With sedatives and dehydration therapy, including the restriction of salt and fluid, and two intramuscular injections of mercupurin (1 and 2 cc., respectively), the patient lost 30 pounds (13.6 Kg.).

Thirteen days after his admission to the hospital and one day after the second injection of mercupurin was given it was noted that the patient was suffering from marked weakness. The following day mental aberration developed, and he became noisy and attempted to strike the nurses. It was necessary to transfer him to another institution. This case is an instance of weakness and psychosis, diagnosed at the time as "psychosis with cardiac disease" following diuresis.

SUMMARY

A clinical picture which may be seen in association with diuresis is described.

The syndrome consists of the following features: weakness, restlessness, mental confusion, apathy, coma and, in some instances, death. All of these features need not be present in a given case.

The syndrome is attributed primarily to the depletion of water and sodium chloride.

The therapy consists in the restoration of water and sodium chloride, preferably by month.

Certain criteria and methods of prophylaxis are suggested. It is stressed that no indictment of the mercurial diuretics or of the various methods of dehydration is intended.

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FUNCTION OF THE LARGE INTESTINE OF MAN IN ABSORPTION AND EXCRETION

STUDY OF A SUBJECT WITH AN ILEOSTOMY STOMA AND AN ISOLATED COLON

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The object of this study was to determine the function of the large intestine as an excretory organ and to consider its probable rôle in absorption under normal conditions. The opportunity for such a study was presented by a young woman who had been subjected to a single barrel permanent ileostomy which had left an isolated large intestine. At operation the ileum, which had been severed close to the ileocecal junction, had been brought out through the abdominal wall. Hereditary polyposis of the colon had constituted the indication for this operation, which had been performed as a preliminary measure to colectomy. This procedure permitted the collection of the excreta of the small intestine, and the products of the isolated colon could be recovered at the same time. In this manner it was possible to determine the composition of the intestinal material that normally is delivered to the large intestine and, by comparison with normal feces, to estimate the changes usually produced by the colon during alimentation. Furthermore, collection of material which originated in the isolated colon during known metabolic periods made it possible to test the validity of current conceptions of the colon as an excretory organ. If the chief value of the intestine in man is in excretion and if this portion of the intestine plays an important part in the excretion of calcium, magnesium and iron, as is stated in textbooks of physiology,[1] an analysis of the products of this isolated colon might reveal such specific functions. The stomach and small intestine of this subject were normal, and, although the colon contained polyps, it

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1. Starling, E. H.: Principles of Human Physiology, ed. 6, Philadelphia, Lea & Febiger, 1933, pp. 1 and 136.

seems reasonable to assume that a specific function of the colonic epithelium in excretion of minerals would not be affected, particularly since a great deal of normal mucous membrane was present and since the pathologic alterations did not suggest an accompanying diminution in the functional ability of the epithelial cells.

THE PLAN OF STUDY

The subject of this study was a woman aged 21 who weighed 100 pounds (45.4 Kg.) and who was 60¾ inches (154.3 cm.) in height. She enjoyed excellent health. During her stay in the hospital collections of the total urine, ileostomy dejecta and colonic products were made during periods in which the total intake was constant and of known amount. For purposes of analysis the collections were divided into three lots, each lot representing the collections made in three days. Carmine markers were used to separate the feces which were passed from the ileum in each period.

TABLE 1.—*Food Eaten in Different Periods*

Type of Food	Amount, Gm.		
	Period 1	Period 2	Period 3
Banana	69	50	50
Orange juice	100	100	100
Tomato juice	100	100	100
Carrots	50	50	50
Bread	55	30	60
Oatmeal	100	50	50
Potato	87	50	50
Rice	100	50	50
Milk	167	100	100
Cream, 20 per cent	180	100	150
Eggs	167	50	50
Steak	94	100	100
Butter	29	40	60
Sugar	22	5	5
Jelly	...	...	30
Coffee	181	100	100
Sodium chloride	5	3.5	3.5
Ferrous sulfate	..	0.3	0.3
Distilled water, cc	1,000	1,000	1,000
Calories	1,914	1,138	1,573

Procedure for the Intake.—The daily intake of food was identical for each day of one three day period, but a change was made for each period. This food, which had a low salt content, was prepared in the same way each time. It was weighed and was entirely consumed. Salt (pure sodium chloride) was added in weighed amounts. The food eaten daily during the three periods is listed in table 1. One thousand cubic centimeters of distilled water also was given every day. All the food was cooked in aluminum vessels to avoid contamination with iron, as it was desired to estimate the amount of iron in the collections. During the last two periods 60 mg. of iron was administered daily by mouth in the form of ferrous sulfate. The intake for twenty-four hours was analyzed for each period. For analysis the food was prepared with that which was served to the patient. A homogeneous suspension of the total diet was made and determinations of the nitrogen, fat and chlorides were obtained with the wet preparation, which obviated the possibility of loss by drying. A large aliquot was dried. Portions of this were converted to ash in the usual manner in platinum dishes, using a muffle furnace with a temperature kept below 500 C. The cal-

cium, magnesium, phosphorus, sodium and potassium in the ash were extracted with hydrochloric acid. For the determination of iron another sample of the food was dried in the presence of sulfuric acid and ashed in a silica dish. The iron was extracted with sulfuric acid. This extract was treated with hydrogen sulfide to remove the copper before the amount of iron was estimated.

Procedure for the Dejecta from the Ileostomy.—The excretions from the abdominal stoma were collected in a rubber pouch the contents of which were removed at intervals; a measured amount of distilled water was used to transfer the contents to suitable containers, which were immediately placed on ice. Carmine markers proved most efficient for the separation of the feces. A homogeneous suspension of the total dejecta was then made, and aliquot portions of the fresh wet substance were analyzed for nitrogen, chloride, fat and carbohydrate. A portion was dried, and aliquot portions of this dry material were converted to ash in a manner similar to that employed in the analysis of the

TABLE 2.—*Chemical Methods Used*

For nitrogen.....	Kjeldahl's macromethod
For chloride.....	Volhard's titration with sulfocyanate indicator after digestion with nitric acid in the presence of silver nitrate [2a]
For fat.....	A modification of the Saxon method [2b]
For carbohydrate.	Hydrolysis with hydrochloric acid; the Shaffer-Hartmann-Somogyi method was used on a phosphotungstic acid filtrate [2c]
For phosphorus...	Method of Fiske and Subbarow [2d]
For calcium.....	Method of Tisdall and Kramer [2e]
For magnesium....	Magnesium was determined on the filtrate which was left after the determination of the calcium; the magnesium was precipitated as magnesium-ammonium phosphate, according to the method of Tisdall and Kramer, and a colorimetric determination of phosphate was made by the method of Fiske and Subbarow
For potassium.....	Precipitation with cobalt nitrate and titration with potassium permanganate, according to the method of Tisdall and Kramer
For sodium.....	Butler and Tuthill's[2f] application of the method of Barber and Kolthoff[2g]
For iron.....	Titration with titanium sulfate, according to the method described by Klumpp [2h]

food. Determinations of calcium, sodium, phosphorus, potassium, magnesium and iron were made on extracts (table 2). The chemical methods referred to in table 2 are described in the literature.[2]

2. (*a*) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 829. (*b*) Saxon, G. J.: A Method for the Determination of the Total Fats of Undried Feces and Other Moist Masses, J. Biol. Chem. **17**:99-102, 1914. (*c*) Shaffer, P. A., and Somogyi, Michael: Copper-Iodometric Reagents for Sugar Determination, ibid. **100**:695-713 (May) 1933. (*d*) Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, ibid. **66**:375-400 (Dec.) 1925. (*e*) Tisdall, F. F., and Kramer, Benjamin: Methods for the Direct Quantitative Determination of Sodium, Potassium, Calcium, and Magnesium in Urine and Stools, ibid. **48**:1-12 (Sept.) 1921. (*f*) Butler, A. M., and Tuthill, Elizabeth: An Application of the Urynal Zinc Acetate Method for Determination of Sodium in Biological Material, ibid. **93**:171-180 (Sept.) 1931. (*g*) Barber, H. H., and Kolthoff, I. M.: A Specific Reagent for the Rapid Gravimetric Determination of Sodium, J. Am. Chem. Soc. **50**:1625-1631 (June) 1928. (*h*) Klumpp, T. G.: The Determination of Iron in Biological Materials, J. Biol. Chem. **107**:213-223 (Oct.) 1934.

Procedure for the Urine.—The twenty-four hour collections of urine were preserved with thymol. Daily estimations of the creatinine were made to serve as an additional check on the accuracy of the collections. Determinations of the chloride, nitrogen and inorganic phosphorus were made directly on the urine. An ash was prepared for determinations of sodium, potassium, calcium, magnesium and iron. Two thousand cubic centimeters of urine was used for the iron determination.

Procedure for the Colon.—After it had been ascertained roentgenographically with a barium sulfate enema that the colon filled easily, it was cleaned out at the beginning of the metabolic period with repeated enemas of warm distilled water, and the return flow was discarded. At the end of three days the process was repeated until the return flow was clear. The fluid was saved. This procedure was repeated at the end of nine days, and the contents were saved. The first collection was made at the end of period 1, and the second collection was

TABLE 3.—*Analysis of the Intake and Output of a Subject with an Ileostomy Stoma*

	Average Daily Value, Gm.										
	Nitrogen	Fat	Carbohydrate as Dextrose	Water	Phosphorus	Chloride	Sodium	Potassium	Magnesium	Calcium	Iron
Period 1, diet 1 (3 days)											
Intake.....	10.28	121	142.0	2,188	.....	4.34	3.54	2.75	0.187	0.579	0.0144
Urine.....	7.52	...	.....	1,070	0.767	2.93	1.02	2.32	0.065	0.274	0.0008
Ileal dejecta	1.37	8	.....	305	0.202	0.57	0.97	0.12	0.007	0.287	0.0075
Output.....	8.89	...	6.7	1,375	0.969	3.50	1.99	2.44	0.162	0.561	0.0078
Balance.....	+1.39	+113	+135.3	+813	+0.141	+0.84	+0.55	+0.31	+0.025	+0.018	
Period 2, diet 2 (3 days)											
Intake.....	6.50	67	93.0	1,782	0.650	2.91	1.09	1.95	0.132	0.322	0.0698
Urine.....	7.70	...	.....	1,022	0.703	2.11	0.51	1.95	0.061	0.202	0.0002
Ileal dejecta	1.19	5	.....	341	0.122	0.74	1.03	0.10	0.064	0.164	0.0566
Output.....	8.89	...	4.2	1,363	0.825	2.85	1.54	2.05	0.125	0.366	0.0568
Balance.....	—2.39	+62	+88.8	+419	—0.175	+0.06	+0.15	—0.10	+0.007	—0.044	
Period 3, diet 3 (3 days)											
Intake.....	7.10	99	126.0	1,734	0.759	3.06	1.74	1.94	0.142	0.377	0.0737
Urine.....	7.31	...	.....	843	0.553	1.96	0.13	1.88	0.057	0.208	0.0001
Ileal dejecta	1.53	6	.....	393	0.171	0.73	1.32	0.17	0.077	0.202	0.0611
Output.....	8.64	...	5.5	1,236	0.724	2.69	1.45	2.05	0.134	0.410	0.0612
Balance.....	—1.54	+93	+120.5	+498	+0.035	+0.37	+0.28	—0.11	+0.008	—0.033	

made at the end of the two subsequent periods. The material obtained was grayish white, and the odor was similar to that of feces. There was no gross blood in the specimens, and their appearance was similar to that of the rectal discharges which the patient had been having on every second or third day before the study was begun. The stools that were passed by rectum without the use of an enema in a later period of two weeks, during which the intake was not controlled, also were analyzed.

RESULTS

The Dejecta from the Ileum.—In table 3 the results of the quantitative estimations made on the food, the urine and the dejecta from the ileum are recorded. As has been said previously, each period was three days in length. The intake, which was the same during each day of a given period, is listed in table 1. It will be noted, however, that the intakes for the three periods differed. The results in table 3 are

expressed in grams and are the average daily values obtained from an analysis of a total collection for three days. All analyses were carried out in duplicate. The material recovered from the isolated colon, although of great interest in this study, has not been included in determining the balance (table 3), since the quantities were not large enough to affect the results significantly. Furthermore, no allowance has been made for excretion through the skin.

If one turns first to a consideration of the utilization of the organic constituents of food, it is seen in table 3 that these substances were well digested and absorbed after they passed through the stomach and small intestine. Thus, in period 1, when the intake was 10.28 Gm. of nitrogen, 121 Gm. of fat and 142 Gm. of carbohydrate daily, the dejecta from the ileum contained only 1.37 Gm. of nitrogen, 8 Gm. of fat and 6.7 Gm. of carbohydrate during each day. The same relative results were obtained in periods 2 and 3, although the quantities were different.

TABLE 4.—*Daily Averages for Dejecta from the Ileostomy Stoma*

	Total Weight, Gm.	Water, Gm.	Percentage of Water	Sodium, Gm.	Sodium Concentration Expressed in Water of Ileal Dejecta, Milliequivalents per Liter	Dry Substance, Gm.	Percentage of Dry Substance	Total Potassium, Gm.	Potassium per 100 Gm. of Dry Substance
Period 1.....	334.4	305	91.3	0.97	138	29.4	8.8	0.122	0.42
Period 2.....	362.9	341	93.9	1.03	131	21.9	6.0	0.103	0.47
Period 3.....	455.1	393	86.4	1.32	146	42.1	13.6	0.170	0.40
Daily average for 9 days.....	384.1	346	90.5	1.11	139	31.1	9.3	0.132	0.43

When the intake and output for each period are compared, it appears that there was a tendency for a greater output of these substances when the intake was large. These differences were not great and are hardly significant.

Noteworthy among the findings was the considerable amount of water in the feces obtained from the ileostomy. In period 1 there was 305 Gm. of water; in period 2, 341 Gm., and in period 3, 393 Gm., in the feces obtained daily from the ileostomy. The material which was passed from the ileum contained from 86.4 to 93.9 per cent of water. In table 4, in which the quantitative estimations are expressed in terms of average daily values, it can be seen that the total weight of the dejecta from the ileum varied from 344.4 to 455.1 Gm. in the three periods, the average for the nine days being 384.1 Gm. These amounts are far in excess of the daily excretions of stools by a normal person. Although the average daily excretion of feces may vary according to the type and amount of food eaten, it usually is approximately 100 Gm.[3] Considering

3. Hawk, P. B., and Bergeim, Olaf: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Sons & Co., 1931, p. 355.

that the normal stools often consist of 70 per cent water and 30 per cent dry substances, it is of interest to calculate the amount of water which the colon would remove from the ileal dejecta should the continuity of intestinal tract in this case be restored. The average daily excretion from the ileostomy stoma during the nine days was 384.1 Gm., and the amount of dry substance in this excretion was 31.1 Gm. (table 4). On this basis, the amount of water which would be present in a normal stool which contained this amount of dry substance would be 72.6 Gm., and the total weight of this theoretical normal stool would be 103.7 Gm. This is approximately a normal amount. Consequently,

TABLE 5.—*Distribution of the Total Daily Output Between Urine and Ileal Dejecta*

Substance	Total Output, Gm.	In Urine		In Ileal Dejecta	
		Gm.	Total Output, %	Gm.	Total Output, %
Period 1					
Phosphorus	0.9720	0.7700	79.2	0.202	20.8
Calcium	0.5610	0.2740	48.8	0.287	51.2
Magnesium	0.1620	0.0650	40.1	0.097	59.9
Potassium	2.4400	2.3200	95.0	0.120	5.0
Sodium	1.9900	1.0200	51.3	0.970	48.7
Chloride	3.5000	2.9300	83.7	0.570	16.3
Iron	0.0078	0.0003	3.6	0.0075	96.4
Period 2					
Phosphorus	0.8250	0.7030	85.2	0.122	14.8
Calcium	0.3690	0.2020	55.2	0.164	44.8
Magnesium	0.1250	0.0610	48.8	0.064	51.2
Potassium	2.0500	1.9500	95.0	0.100	5.0
Sodium	1.5400	0.5100	33.1	1.030	66.9
Chloride	2.8500	2.1100	74.0	0.740	26.0
Iron	0.0568	0.0002	0.3	0.0566	99.7
Period 3					
Phosphorus	0.7240	0.5530	76.4	0.171	23.6
Calcium	0.4100	0.2080	50.7	0.202	49.3
Magnesium	0.1340	0.0570	42.5	0.077	57.5
Potassium	2.0500	1.8800	91.7	0.170	8.3
Sodium	1.4500	0.1320	9.1	1.320	90.9
Chloride	2.6900	1.9600	72.9	0.730	27.1
Iron	0.0612	0.0001	0.1	0.0611	99.9

it is obvious that the excessive weight of the ileal excreta was the result of the considerable amount of water which was present. Removal of this water is a function of the large intestine. One function of the colon, therefore, has been indicated, namely, the absorption of water.

As arresting as was the large amount of water in the material collected from the ileum was the quantity of sodium. In table 3 it is noticeable that the amounts of sodium recovered in the ileal dejecta were great. Table 5, in which the distribution of the total output of sodium in the urine and in the ileal dejecta is recorded, vividly shows the situation in regard to the excretion of sodium. When it is recalled that only 1 or 2 per cent of the total daily output of sodium is normally found in the feces,[4] the presence of from 48.7 to 90.9 per cent of the

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 766.

total output of sodium in the ileal material is of great interest. In this case the sodium was eliminated in large part through the gastro-intestinal tract, and the urine contained relatively little sodium (table 3). This increase in the fecal excretion of sodium, which has been shown by Holt, Courtney and Fales [5] and by us to obtain in diarrheal disease, will be considered in a subsequent report. In diarrheal disease it may be presumed that there is a decreased absorption of fluids by the colon. The small amounts of sodium which were excreted in the urine (1.02 Gm. in period 1 and 0.13 Gm. in period 3) demonstrate that there is a mechanism which tends to preserve the total base in the bodily fluids. The inorganic constituents of the blood serum of this subject were found to be normal on several occasions, which would be expected in the state of health which she maintained. The results of the analysis of the urine excellently demonstrate the ability of the organism to compensate, at least within limits, for the loss of base through the gastro-intestinal tract. The excretion of potassium, however, was not greater in the ileal material than it is in normal feces; only from 5 to 8.3 per cent of the total amount of potassium excreted daily was present in the ileal material. It has been interesting to determine the circumstances attending the output of sodium and potassium in these watery intestinal excreta, in accordance with the suggestion of Peters.[6] In table 4 it may be seen that the excretion of sodium was directly proportional to the output of water in each of the periods of metabolic study, although the amounts of each substance excreted differed from one period to another.

In order to demonstrate the regularity of this finding, the concentration of sodium in the total water of the ileal dejecta has been calculated in milliequivalents per liter (table 4). These concentrations were fairly constant; they ranged from 138 milliequivalents per liter in period 1 to 146 milliequivalents per liter in period 3, the average daily value for the nine days being 139 milliequivalents per liter. On the other hand, the output of potassium was proportional to the total dry substance (table 4). The concentration of potassium in the total dry substance was fairly constant. Although there was an increase in the amount of water and sodium of the ileal dejecta in period 2 over period 1, the amount of potassium decreased, and accompanying this decrease there was less total dry substance in period 2 than in period 1. The distribution of chloride between the urine and the gastro-intestinal excretion also was disturbed (table 5) but to a less extent than was the distribution of sodium. Whereas in normal feces the loss of chloride is insignificant, in this case from 16.3 to 27.1 per cent of the

5. Holt, L. E.; Courtney, Angelia M., and Fales, Helen L.: The Chemical Composition of Diarrheal as Compared with Normal Stools in Infants, Am. J. Dis. Child. **9**:213-224 (March) 1915.

6. Peters, J. P.: The Distribution and Movement of Water and Solutes in the Human Body, Yale J. Biol. Med. **5**:431-467 (May) 1933.

total output of chloride occurred through the intestinal tract. This loss of chloride occurs also in diarrheal disease, as does the loss of sodium.[5]

A consideration of the amounts of sodium, potassium and chloride which were found in the ileal excreta presents several interesting facts. In the first place, it is apparently a function of the colon to absorb in solution this excess of sodium and chloride and probably a certain amount of other minerals, in order to convert into normal feces the material delivered from the ileum. This represents one of the important functions of the colon—the conservation of the total electrolyte and fluid of the body. But it cannot be said that this is an indispensable function, since in the presence of losses from the gastrointestinal tract there is a marked decrease of the urinary output of these substances and the serum electrolyte still is maintained at a normal level. In the absence of the colon the maintenance of an adequate intake of minerals becomes more important than it is in cases in which the colon is present. Second, it has been shown that in the ileostomy dejecta, which are comparable to a diarrheal stool in many respects, the elimination of sodium is proportional to the excretion of water and that the excretion of potassium is proportional to the output of total solids. Since potassium is the predominant base in the cells of man and because the fecal excretion of potassium varies with the total solids of the excreta, the greater excretion of potassium than of sodium in normal feces probably is the result of the cellular origin of the former rather than of any selective impermeability of the intestinal tract. Peters [6] has suggested such an explanation for the relatively large amount of potassium in normal feces, and it is a reasonable one, if it may be presumed that potassium is the predominant base of bacteria. Steele [7] found that the bacterial content of all types of feces may be as great as 38 per cent of the dry weight, and he said that Strasburger estimated that from a third to a fourth of the dry weight of normal feces was due to bacteria. In addition to bacteria, there is a variable amount of epithelial cells from the lining of the intestine. By reference to table 3 it will be noted that the concentration of sodium expressed in the total water of the dejecta of the small intestine of this patient, which varied from 131 to 146 milliequivalents per liter, is somewhat similar to the concentration of sodium in the blood serum and intestinal fluid. Recently, DeBeer, Johnston and Wilson,[8] who have examined the composition of the secretions obtained at various levels of the intestinal tract of the dog, have found that the concentration of sodium is relatively constant

7. Steele, J. D.: The Method of Determining the Total Amount of the Fecal Bacteria by Weight and Its Clinical Significance, J. A. M. A. **49**:647-649 (Aug. 24) 1907.

8. DeBeer, E. J.; Johnston, C. G., and Wilson, D. W.: The Composition of Intestinal Secretions, J. Biol. Chem. **108**:113-120 (Jan.) 1935.

in succus entericus from the small and large intestines and that it is similar to the concentration of sodium in blood serum (from 146 to 156 milliequivalents per liter). The chloride in ileal secretions was found by these investigators to be from 73 to 87 milliequivalents per liter. In the present case the concentration of chloride expressed in the total water of the ileal dejecta varied from 52.5 to 55.4 milliequivalents per liter. While the values for sodium obtained by DeBeer, Johnston and Wilson demonstrated the similarity between the amounts of sodium in blood serum and in intestinal fluid, values for the chloride in the intestinal contents are lower than those for the chloride in the blood serum. The acid component of intestinal fluid at the ileum is made up in large part by bicarbonate,[8] a fact which explains why the relative loss of chloride is less than that of sodium in the watery excretion of the ileum in the present study.

Whether this expression of the sodium in the water of the ileal dejecta represents the condition that obtains was investigated during controlled periods subsequent to the completion of the study. Collections of fresh excreta from the ileostomy stoma were secured and centrifugated at high speed, and the clear supernatant liquid was decanted and filtered. The concentration of sodium in this fluid was found to be 132.8 and 123.3 milliequivalents per liter, respectively, on two different occasions. The concentration of potassium in these same specimens of supernatant fluid was 4.5 and 4.8 milliequivalents per liter, respectively. The concentration of chloride in these same specimens was found to be 79.7 and 84.5 milliequivalents per liter, respectively.

These considerations give the impression that during the process of alimentation the ileum delivers to the colon its solids and a variable amount of fluid which is probably near osmotic equilibrium with the blood. This fluid and its soluble constituents are then in large part absorbed by the colon.

The distribution of the excretion of the other inorganic constituents (magnesium, phosphorus and calcium) between urine and feces is not remarkable, as there was no demonstrable deviation from the normal, except possibly in the case of calcium, the urinary output of which was somewhat larger than usual (table 5). The variability of the excretion of calcium in the urine of normal persons is well known and depends on several factors, which have been pointed out by Bauer, Albright and Aub.[9]

Material Recovered from the Isolated Colon.—The results of the analyses of the material which had accumulated in the isolated colon during these metabolic periods are recorded in table 6 *A*. The amounts

9. Bauer, W.; Albright, F., and Aub, J. G.: Studies of Calcium and Phosphorus Metabolism: Calcium Excretion of Normal Individuals on Low Calcium Diet; Also Data on Case of Pregnancy, J. Clin. Investigation **7**:75-96 (April) 1929.

of substances recorded for period 1 were secured at the end of period 1 of the metabolic study. Under the heading period 2 are tabulated the amounts recovered during periods 2 and 3 of the metabolic study. Obviously, these weights, when calculated in terms of daily values, would not add a significant amount to the total output and do not materially affect the balance, as has been mentioned previously in connection with a description of table 3. The striking gross finding is that a small amount of any substance was recovered during the first three days and the second six days. The amounts of total nitrogen and chloride were small. A relatively large amount of potassium was recovered during both periods. This again suggests the cellular origin of this base in feces. In the

TABLE 6.—*Analysis of Material Recovered from the Isolated Colon*

A. During Metabolic Study

	Period 1: Three Day Total, Gm.	Period 2: Six Day Total, Gm.
Nitrogen	0.11100	0.1330
Chloride	0.04800	0.1980
Sodium	0.02700	0.1330
Potassium	0.10600	0.1980
Calcium	0.01500	0.0130
Phosphorus	0.01600	0.0180
Magnesium	0.00200	0.0020
Iron	0.00053	0.0013

B. During a Two Week Uncontrolled Period

	Fourteen Day Total, Gm.
Weight of total substance	65.0000
Dry weight	4.3700
Nitrogen	1.4000
Chloride	0.1190
Calcium	0.0350
Sodium	0.0420
Potassium	0.4030
Magnesium	0.0050
Phosphorus	0.0350
Iron	0.0009

second period (six days) the amount of sodium was relatively large. Of particular note were the amounts of calcium and iron which were recovered. During the first three days a total of 15 mg. of calcium and approximately 0.5 mg. of iron was obtained from the isolated colon. These amounts, were they to be expressed in amounts recovered daily, would be small, indeed. From the results of these analyses of colonic material it appears that either the colon has no special function that is related to the excretion of these minerals or the method which has been used, namely, the diversion of the intestinal stream, has altered its ability in this regard. The latter would be a change, however, that would not be expected if the colon possessed a specific excretory mechanism. In this study, in which ample time was allowed for large quantities of calcium and iron to collect in the colon should this portion of the intestine be the particular site for their elimination, it has been found that no such condition obtains. The quantities of each substance are not large enough

to warrant the assigning of any specific function of the colon in their excretion. Comparing, in period 1, a recovery of 5 mg. of calcium with a total output of 561 mg. of calcium daily indicates the minor importance of the large intestine as an excretory organ (table 3). Likewise, in the case of iron approximately 0.5 mg. was recovered in three days in period 1, yet 23.4 mg. was excreted in the urine and feces during the same time. During the following six days approximately 1 mg. of iron was recovered during the entire time, yet the intake was approximately 70 mg. of iron daily, largely in the inorganic form (see table 3). During the time of the feeding of additional iron (periods 2 and 3) a large amount was recovered from the ileostomy dejecta. The amount of iron in the urine was not increased by this added intake of iron, the daily amount being only 0.2 mg. for period 2 and 0.1 mg. for period 3. Gottlieb in 1890[10] demonstrated that the amount of iron in the urine is small and that it is not increased by the feeding of large amounts of iron.

As our patient had discharges of material from the rectum every two or three days which simulated normal bowel movements, it was felt that analysis of this material passed from the rectum without the aid of enemas would furnish additional information, particularly since this method would obviate the use of a possibly disturbing factor. Accordingly, the dejecta were collected for two weeks when the subject was not under controlled conditions of intake but on a normal regimen, except for the addition of 60 mg. of iron daily (in the form of ferrous sulfate) during the first week. The weight of the total dejecta from the isolated colon during these two weeks was 65 Gm. Analysis of the dejecta is recorded in table 6 *B*. It is again apparent from the results obtained in the analysis of the excretory product of this isolated colon that the large intestine under these conditions possesses no special function in excretion. The total amount of calcium excreted from the isolated colon in fourteen days was only 35 mg., and the amount of iron was only 0.9 mg.

COMMENT

The Dejecta from the Ileum.—The results obtained in this study have shown that the protein (as indicated by nitrogen values), fat and carbohydrate are well absorbed in their passage through the stomach and small intestine. The amounts of nitrogen, fat and carbohydrate (table 3) found in the ileal dejecta are similar to the quantities of these substances usually found in normal stools.[11]

10. Gottlieb, R.: Beiträge zur Kenntnis der Eisenausscheidung durch den Harn, Arch. f. exper. Path. u. Pharmakol. **26**:139-146, 1890.

11. Taylor, A. E.: Digestion and Metabolism: The Physiological and Pathological Chemistry of Nutrition, Philadelphia, Lea & Febiger, 1912, pp. 212 and 215.

There is a general indication in the literature [12] that the digestion and absorption of the various organic portions of the food is completed before the food reaches the large intestine, as the results in this study also have shown.

In the case of the inorganic constituents of the ileostomy dejecta no comparable studies have been found with which the results obtained may be compared. The amounts of calcium, magnesium, phosphorus and iron excreted from the ileum would not be unusual in normal feces under similar conditions of intake. Such a situation does not obtain in the case of the excretion of sodium and chloride, however. The most significant findings in the examination of the dejecta from the ileostomy stoma were the large amount of sodium and chloride delivered to the colon for absorption and the indication that this sodium is present largely in the fluid portion of the ileal excretion and that the fluid component of the total material at the ileum is probably in osmotic equilibrium with the blood. The low concentration of potassium in the fluid portion of the ileal excretion in the presence of a fairly large total amount of potassium has intimated some reason for the relatively large amount of this mineral in normal stools and has formed the basis for additional work on this subject.

Material Recovered from the Isolated Colon.—As the results obtained in this present study indicate that the colon has no specific function in excretion, it has been of interest to review the works usually cited as evidence to the contrary. Calcium and iron are the two minerals almost universally considered to be excreted by the large intestine, and they will be considered in detail.

The Excretion of Calcium by the Colon.—There is no doubt that calcium is lost from the body through the feces. The early studies on starving men by Lehmann and Friedrich Mueller and their colleagues [13] demonstrated this fact, and numerous workers since have shown that feces normally contain calcium and that the larger loss of calcium usually occurs through the feces rather than through the urine. Donald Hunter,[14] in his review of the metabolism of calcium and phosphorus,

12. Canavero, M.: Studio dell'assorbimento dei grassie delle sostanze proteiche dopo la colectomia (ricerche sperimentali), Policlinico (sez. chir.) **40**:629-641 (Nov.) 1933. Heile, B.: Experimentelle Beobachtungen über die Resorption im Dünn- und Dickdarm, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:474-486, 1905. Landt, H., and Daum, K.: Physical Characteristics of Residues from the Small Intestine, Arch. Int. Med. **52**:96-104 (July) 1933.

13. Lehmann, Curt; Mueller, Friedrich; Munk, Immanuel; Senator, H., and Zuntz, N.: Untersuchungen an zwei hungernden Menschen, Virchows Arch. f. path. Anat. (supp.) **131**:107, 1893.

14. Hunter, Donald: Critical Review: The Metabolism of Calcium and Phosphorus and the Parathyroids in Health and Disease, Quart. J. Med. **24**:393-446 (April) 1931.

said that it is generally accepted that calcium is eliminated by the large intestine and to a less extent by the kidneys. Various investigators have studied the subject of calcium excretion by the large intestine, and their work represents the basis for the statements that the colon is a more important site for the elimination of this mineral from the body than is the small intestine. Walsh and Ivy [15] have determined the calcium content of various loops of the small and large intestine in dogs and have concluded that calcium is eliminated to a much greater extent by the mucosa of the large intestine than by the mucosa of the small intestine. In their experiments, by using distilled water as an irrigating fluid to recover calcium from surgically isolated loops of intestine, they recovered more calcium from the colon than they did from portions of the small intestine. Stewart and Percival,[16] who used cats in somewhat similar experiments, have concluded that there is a specific mechanism in the colon for the excretion of calcium and that the large intestine provides the main excretory route for this mineral. Taylor and Fine,[17] who used physiologic solution of sodium chloride for irrigation because they found that distilled water irritated the intestinal mucosa, obtained much less calcium from the colon than did the previous investigators. This suggests that an important difference in the results occurs when the irrigating fluid is isotonic.

A possible objection to the method used in these experiments, which depended on irrigation of an intestinal loop with distilled water at more or less frequent intervals, is that this water may accomplish more than its purpose intends. Not only may the minerals secreted into the lumen be washed out, but a certain amount of electrolyte also may diffuse from the intestinal wall into the distilled water. An attempt to establish an equilibrium, one of the steps preceding absorption, may be initiated. In this instance, the length of time that water is permitted to rest in the lumen of the intestine and the number of irrigations given in a stated time become factors. Furthermore, it seems that the dimensions of the surface area of mucous membrane irrigated in each of the segments of intestine is an important consideration if comparisons are to be made of a differentiating nature. In the present study a lapse of three and of six days was allowed for the products which originate in the colon to accumulate, in order to avoid these possible effects of frequent washing. To test the validity of the contention that frequent

15. Walsh, E. L., and Ivy, A. C.: Calcium Excretion by the Alimentary Tract, Proc. Soc. Exper. Biol. & Med. **25**:839-840, 1928.

16. Stewart, C. P., and Percival, G. H.: Studies on Calcium Metabolism: I. The Action of the Parathyroid Hormone on the Calcium Content of the Serum and on the Absorption and Excretion of Calcium, Biochem. J. **21**:301-313, 1927.

17. Taylor, N. B., and Fine, A.: The Excretion of Calcium Through the Intestine, Am. J. Physiol. **93**:544-553 (June) 1930.

irrigation of the colon results in the recovery of a large amount of calcium, four enemas of distilled water were given to the subject within a period of two hours after a preliminary cleansing. The filtrable portion of the returns from the enemas contained 22 mg. of calcium (more than was recovered in three days during the study), which indicates the importance of a factor which may have influenced the results obtained by other investigators.

It has been stated that the largest elimination of calcium from the body occurs through the gastro-intestinal tract. The amounts in feces, which represent the excreted portion and the unabsorbed component, cannot be satisfactorily evaluated. It seems that the mechanism by which calcium is excreted in the gastro-intestinal tract might depend on the relative insolubility of its salts, just as does the difficulty of its absorption. Opportunities for the excretion of calcium seem to be greatest in the small intestine, where the extensive chemical changes are proceeding and where great changes in the electrolytes and fluids are in progress. The large amount of intestinal juices poured into the lumen of the small intestine probably contributes in large part to the formation of this insoluble calcium. Calcium will tend to be precipitated particularly in the lower part of the small intestine where the medium is more alkaline.[18] This precipitation of calcium from the intestinal fluid could occur also in the colon, since a considerable amount of calcium is delivered to it from the small intestine. The amount of calcium actually added to the material in the lumen of the colon from the body fluids is expected to be small, when one considers that the fluid delivered to the colon is probably near equilibrium with the blood and that little diffusion of calcium from the latter would be expected. Furthermore, the colon does not produce an important amount of succus entericus, which could be a source of the addition of some calcium to feces.

Heupke,[19] in summarizing his study of the excretory products of the isolated colon in the dog, concluded that the rôle of the large intestine in excretion is minor, and he stated that he believed that the largest part of the mineral constituents of the feces, as far as they are not the unabsorbed residue of food, are excreted in the small intestine.

The Excretion of Iron by the Colon.—Robscheit-Robbins[20] has stated the present day conception of the absorption and excretion of iron, which is that this substance is absorbed in the entire gastro-intestinal tract, although the duodenum and some of the upper portion

18. Mann, F. C., and Bollmann, J. L.: The Reaction of the Content of the Gastro-Intestinal Tract, J. A. M. A. **95**:1722-1724 (Dec. 6) 1930.

19. Heupke, W.: Ueber die Sekretion und Excretion des Dickdarmes, Ztschr. f. d. ges. exper. Med. **75**:83-125, 1931.

20. Robscheit-Robbins, F. S.: The Regeneration of Hemoglobin and Erythrocytes, Physiol. Rev. **9**:666-709 (Oct.) 1929.

of the gastro-intestinal tract play the major rôle. Excretion likewise is largely by the intestinal route, the colon being its site for the great part. Early work on animals by Bidder and Schmidt [21] demonstrated that the greater part of the excretion of iron occurs in the feces. Lehmann and Friedrich Mueller and their colleagues in a study of fasting men, in 1893, demonstrated a daily excretion of 7 and 8 mg. of iron, respectively, in the cases of Cetti and Breithaup. Gottlieb [22] showed that 70 per cent of the iron administered subcutaneously to dogs could be recovered in the feces. A great deal of investigation on the excretion of iron was carried out in the last half of the nineteenth century by German workers. Certain studies, notably those of Hochhaus and Quincke,[23] ascribed the greatest rôle in excretion of iron to the large intestine. As early as 1906, however, Meyer [24] critically reviewed the literature on this subject and, in evaluating it, was unable to find that the site of the excretion of iron in the intestine had been determined. Meyer, however, was impressed by the work of Kobert and Koch,[25] who studied the excretory products of a large segment of isolated colon of a human subject. Kobert and Koch recovered only about 1 mg. of iron daily from the colon. The experiments of Chevalier [26] in 1914 indicated that the small intestine is the more important site of excretion of iron. M'Gowan [27] has recently reviewed this subject of the movements of iron in the body, and his experimental work with the fowl has shown that the process of excretion of iron is more intense in the duodenum than elsewhere and that it becomes progressively less marked throughout the rest of the intestinal tract.

SUMMARY

In this study of a human subject with an ileostomy stoma and an isolated colon the material which was excreted from the ileum was examined in order to determine the composition of the intestinal material delivered to the large intestine. At the same time the substances which

21. Bidder, F., and Schmidt, C.: Die Verdauungssäfte und der Stoffwechsel: Eine physiologisch-chemische Untersuchung, Leipzig, G. A. Reyher, 1852.

22. Gottlieb, R.: Ueber die Ausscheidungsverhältnisse des Eisens, Ztschr. f. physiol. Chem. **15**:371-386, 1891.

23. Hochhaus, H., and Quincke, H.: Ueber Eisen-Resorption und Ausscheidung im Darmkanal, Arch. f. exper. Path. u. Pharmakol. **37**:159-182, 1896.

24. Meyer, Erich: Ueber die Resorption und Ausscheidung des Eisens, Ergebn. d. Physiol. **5**:698-745, 1906.

25. Kobert, R., and Koch, W.: Einiges über die Functionen des menschlichen Dickdarmes, Deutsche med. Wchnschr. **47**:883-886 (Nov. 22) 1894.

26. Chevalier, Paul: Recherches sur l'élimination intestinale du fer, Arch. de méd. expér. et d'anat. path. **26**:277-305 (May) 1914.

27. M'Gowan, J. P.: The Absorption and Excretion of Iron by the Intestines and the Nutritional and Therapeutic Value of Its Salts, Edinburgh M. J. **37**: 85-96 (Feb.) 1930.

accumulated in the isolated colon during known metabolic periods were determined in order to estimate the importance of this section of the intestinal tract in excretion.

The data obtained have demonstrated that the organic constituents of the food are digested and absorbed before they reach the colon and that the ileum delivers to the colon solid material and a variable amount of fluid which seems to be near osmotic equilibrium with the blood. This ileal material contains a large amount of sodium and chloride when compared with normal feces. A function of the colon in the absorption of electrolyte and water has been indicated.

It appears that the human colon has no specific function in the excretion of minerals. Particularly has it been indicated that no substantial amounts of calcium or iron were recovered from the isolated colon.

The suggestion is offered that it is probable that variable amounts of cellular débris and bacteria may be added to the intestinal contents in the colon, thus augmenting the total mass which ultimately becomes feces. Such a possibility, however, hardly falls into the category of a specific function.

Progress in Internal Medicine

REVIEW OF NEUROLOGY AND PSYCHIATRY FOR 1935-1936

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HEREDITY

The inheritance of nervous diseases has long been a question which has attracted interest. The fear of inheriting epilepsy or insanity still haunts many persons unnecessarily. Fortunately, scientific investigation is beginning to clarify the problem, and recent political events, such as the Nazi drive for "race purity," have made the problem a timely issue. Since May 1934 a committee of the American Neurological Association has been at work evaluating available data, and a preliminary report on sterilization has been made to the association. The chairman, Dr. Abraham Myerson, has had wide experience in this field and has been assisted by a professional geneticist, Dr. Keeler, and three neurologists, Drs. Ayer, Putnam and Alexander. The report [1] makes a pamphlet of one hundred and thirty-two pages and is full of important data, references and good sense.

Of course there is no doubt about the inheritance of certain neurologic disorders, such as Huntington's chorea, Friedreich's ataxia, hypertrophic neuritis, Leber's atrophy of the optic nerve, atrophy of the peroneal muscles, the muscular dystrophies and paroxysmal paralysis.

In many of these both the lesion and the type of inheritance are well known. But when the discussion turns to such doubtful entities as feeblemindedness, epilepsy and schizophrenia, the situation is quite different. The especial stumbling block has been a vague, undefined concept known as neuropathic inheritance or degeneracy. All manner of mental diseases and neurologic disorders and all psychoses, including feeblemindedness, epilepsy and crime, are thus labeled. Up to the present day this doctrine prevails in most of the studies made on the heredity of mental disease, and until lately, under a new guise in the mendelian work it has been given the sanction of the foremost writers. In the excessive development given this theory, headache in an ancestor was given a hereditary value in relation to the mental disease of his descendants. Fainting spells even in a cousin had a dread significance,

1. Report of the Committee for the Investigation of Sterilization, American Neurological Association, Boston, 1935.

and the early writers laid great stress on tuberculosis, cancer, hemiplegia, gout, "rheumatism" and every chronic or semichronic ailment. In other words, any ill that relatives have suffered from that might be called "nervous" has been considered significant. This adding up of unlike traits, of varied polymorphic characters, is about as scientific as the old ornithologic grouping of the birds as "those principally black in color," those "with conspicuous blue plumage" and so forth. The science of genetics, with its new understanding of unit characters, shows that all problems of inheritance need careful analysis, with a meticulous definition of the terms. "While a certain possible trend toward polymorphism may be found and while it is possible that the constitution in which, for instance, epilepsy develops has some relationship to the constitution in which dementia praecox develops, the relationship is not close enough to warrant belief in a general unitary trait back of all psychoses, feeblemindedness, epilepsy and the like. Consequently, a great deal of the work which has been done is entirely invalid and has only historical significance." This is the conclusion reached by Genil-Perrin in an exhaustive study of the history and the effect of the theory of mental degeneration, which deserves a wider recognition than it has received.

One of the commonest medical misconceptions current among the general population and even among physicians is that epilepsy is an inherited disease leading to mental deterioration. In the first place, the word epilepsy merely signifies that the victim suffers from recurrent seizures. These fits may be caused by any one of fifty or more pathologic conditions, and by far the larger number of these conditions are acquired and therefore not inheritable. Probably the greatest cause of epilepsy is cerebral trauma (at birth or later), closely followed in importance by infections of the brain and meninges in infancy and youth. It is obvious, therefore, that if a young sufferer from convulsions asks a physician if he or she may marry, the physician must look up the individual case and if possible determine the etiology of the convulsions before having the slightest scientific right to answer the patient's important query. Of course, there are families in which fits appear as an inherited character, but these are relatively rare. Taking a group of 1,000 patients with epilepsy, Stein [2] found that they had 6,572 parents, siblings and children. Of these, 3.7 per cent had fits, while in a control group only 1.3 per cent gave such a history. Fits occurred in 2.3 per cent of the fathers of epileptic patients and in 3.5 per cent of the mothers, while in the fathers or mothers of the controls the rate was approximately the same as that for the general population (0.35 per cent). In general, then, it may be said that seizures do

2. Stein, C.: Am. J. Psychiat. **12**:989, 1933.

occur about four times as often in all or any relatives of epileptic patients as in control groups. But even this low figure is an average, and in dealing with an individual patient this means nothing. An epileptic patient belongs either to the large group whose inheritance is perfectly good or to the small group whose inheritance is distinctly bad and should preclude marriage; this can be determined only by a careful investigation of the family tree. There is, however, an exception to this clear statment; i. e., even among the patients in whom epilepsy is known to be due to trauma, there is a somewhat more definite family incidence of fits than in a control group.[3] In other words, certain families are more likely to react to cerebral lesions by exhibiting epileptiform seizures than are other families, which might react with headache or with dyspepsia. Only in this limited way can the theory of neuropathic inheritance be reasonably invoked.

The outstanding defect in all the discussion on feeblemindedness and its heredity has been the tendency to lump all types of feeblemindedness together and to discuss feeblemindedness as if it were a unit. A preliminary consideration of the subject matter shows that the cases of feeblemindedness may be divided into several main groups: (1) those in which the condition is due to sporadic cretinism, (2) those in which it is due to mongolian imbecility, (3) those in which it can fairly well be traced to injury to the brain at birth or to infectious disease shortly after birth, (4) those of so-called syphilitic feeblemindedness, (5) those in which the condition is due to microcephalus and hydrocephalus, (6) those in which it is due to amaurotic idiocy and (7) the vast mass of cases of feeblemindedness in which no definite lesions are found and which become known only as a lowered mentality becomes manifest. It is in this unclassified group that one finds the families whose members are feebleminded. From whatever angle feeblemindedness is approached, if one excludes cretinism, mongolism and other differentiated types of feeblemindedness, the results of the various studies show a larger proportion of inheritance of feeblemindedness than could be expected by any law of chance; in other words, in a considerable segment of feeblemindedness heredity plays a rôle of importance. It does not appear in the more careful studies that mental diseases and epilepsy are fundamentally related to feeblemindedness in a biologic sense. Furthermore, authors on the whole agree that feeblemindedness when hereditary cannot be considered as a simple mendelian recessive character and that if there is a mendelian inheritance it is multifactorial which means, on the whole, that it is practically impossible to predict the results of sterilization of the feebleminded.

3. Lennox, W. G., in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1933, vol. 6, chap. 31.

It is curious to note that, while the literature is unanimous as to the hereditary character of manic-depressive psychosis, little valuable statistical material is available. Many authors present only charts of selected and particularly highly tainted families. The character is generally considered to be dominant. However, it must be stated that the figure obtained lags behind that which one would expect, and the term irregular dominance might fit the biologic situation better. In a recent paper Rüdin states as his conclusion that the incidence of manic-depressive psychosis is twenty-five times as high among the siblings of manic-depressive patients as in the average population. The most recent German study on the subject is that of Luxenburger. He gives about the same figures as Rüdin and Hoffmann, namely, a probability for the development of the disease in 32 per cent of the children of manic-depressive parents. Where practical eugenics is concerned, however, Luxenburger advises great precaution and points to the fact that from the marriages of manic-depressive couples children may emerge who do not have the genotype for manic-depressive insanity but present only partial characters of it, which may be of great positive social and eugenic value. He emphasizes the principle of *Nicht schaden!* (do no damage) and advises a strongly individual consideration in every case. Luxenburger himself points to the fact that manic-depressive subjects as a group are socially productive and successful. He demonstrates clearly that in the families of manic-depressive subjects there are about four times as many members of the higher social strata as in the average population (23.3 per cent: 8.7 per cent). It is safe to say that manic-depressive psychosis is inheritable and that whether in mild or severe form it becomes manifest in many of the descendants of those who have the disease.

Rosanoff and his associates[4] have brought additional evidence, through the study of identical twins, that manic-depressive psychosis is the most hereditary of the commoner mental diseases. In a series of twenty-three pairs of monozygotic twins both had manic-depressive psychosis in sixteen instances and only one of a pair in seven instances. A series of sixty-seven pairs of dizygotic twins showed both affected by this psychosis in eleven cases and only one affected in fifty-six instances. In other words, 70 per cent of the monozygotic and 16 per cent of the dizygotic pairs were both affected.

SCHIZOPHRENIA (DEMENTIA PRAECOX, PARERGASIA)

During the year 1935 two hundred and twenty-nine papers and two books were published on schizophrenia. This fact is noted in order to give an idea of the mass of research that is being directed toward

4. Rosanoff, A. J.; Handy, L. M., and Plesset, I. R.: Am. J. Psychiat. **91**:725, 1935.

the elucidation of one of the most difficult problems in medicine, a problem which economically ranks ahead of tuberculosis and cancer when the situation is envisaged in units of days spent in a hospital. In his chapter on the social significance of psychiatry, White [5] shows that in 1933 there were a total of 296,000,000 so-called hospital days in the United States. Of these, 146,000,000 were used by "mental" patients (exclusive of the epileptic and feebleminded). From the general run of the diagnoses in hospitals for patients with mental disorders, one knows that about half the "insane" are suffering from schizophrenia (with the aforementioned exclusions), necessitating a total of approximately 73,000,000 hospital days, which approaches the total for all general diseases combined (85,000,000) and is more than three times as great as that for tuberculosis (22,000,000).

Having stated how prevalent schizophrenia is, one's next duty is to define it. This is difficult because of its many manifestations and because patients with marked schizophrenic symptoms often show some disturbances usually attributed to other diseases. In a practical classification based on personality Meyer [6] describes the disease as one in which there is a personality disorder mainly in the content of thought. There is fixation on topics, with false systematization of ideas; thinking is along lines not acceptable to the average intelligent member of the patient's social group. This is in contrast to the disorders of mood, in which the personality is dominated for long periods by moods of sadness or elation.

Kretschmer considers the problem from the point of view of types of character and says that persons with schizoid characteristics are classifiable into three groups: (1) unsociable and eccentric persons who are devoid of humor; (2) timid, sensitive, excitable lovers of books and (3) docile, stupid persons. "As the cycloid temperament lies between the poles of gaiety and sadness so does the schizoid lie between those of instability and dullness." Bleuler speaks of schizophrenia as a physical illness with a prolonged course, having a superstructure of psychogenic origin determined by the patient's experiences. The thought processes of the schizophrenic patient are characterized by logically unrelated ideas that are related in the patient's mind, a condensation of ideas, unusual symbolization, vagueness and alliteration. These lead to delusions, hallucinations, negativism, stereotyped behavior and catatonia.

In cases of definite schizophrenia some of the signs and symptoms commonly observed are fever, fatigue, headache, cyanosis of the extrem-

5. White, W. A.: Twentieth Century Psychiatry, New York, W. W. Norton & Company, Inc., 1936.

6. Meyer, A., quoted by Muncie, W., and White, P.: The Mood-Content Problem and Thymonoic Reactions, Arch. Neurol. & Psychiat., to be published.

ities, low blood pressure, low basal metabolic rate, pupillary disturbances, vasomotor disorders and convulsions. It is useless to argue as to which is primary—the physical or the mental. Biochemical and structural changes are active components in any disorder.

This is all ably discussed and summarized in a book by Lewis,[7] just issued by the Northern Masonic Jurisdiction of the Scottish Rite. The author carefully reviews a vast literature and summarizes the trends, giving excellent bibliographies. The clinical features are discussed at length. Under the heading psychologic Freud's concept is emphasized—that one must consider three categories of factors: (1) heredity, the sum total of the constitutional equipment of the subject; (2) disposition, due to early environmental influences, and (3) immediate environment. In psychoanalytic idiom, the narcissistic features are of the most interest psychologically. The patient becomes so interested in contemplating himself that he withdraws his interest from the outside world and regresses, sometimes to stupor. Patients who have gone through such stupors not infrequently recover, and some regain enough contact with the physician to describe their experiences. Often their extreme preoccupation was due to fantasies concerning their reproductive and eliminative functions—strange ideas about urine, feces, semen and birth often come out in a startling way. No one who listens to these accounts can help being impressed by their similarity to the types of primitive thinking described by Freud. Even if the patient does not talk, his behavior often clearly indicates his preoccupation with the genitals and excreta. Nevertheless the concept of narcissism is too narrow. In many instances the patient's fantasies are not directed toward his own body.

Jung[8] thinks these fantasies may sometimes come from the deepest level of unconsciousness, the level where the history of the human race is inherited in a "collective unconscious," so that similar delusions, like similar folk myths, arise in different parts of the world.

Hoffmann[9] is of the opinion that the reaction type of the schizophrenic patient is predetermined in some way. The "logical superstructure" loses its control and position in the thought structure, thus allowing the archaic-primitive type of thinking to come to the foreground and to appear as expressions of psychotic symptoms. Hoffmann points out that the characteristic appearance of the body types, including the pyknic, asthenic and dysplastic, fortifies the impression that the bio-

7. Lewis, N. D. C.: Research in Dementia Praecox, New York, National Committee for Mental Hygiene, 1936.

8. Jung, C. G.: Modern Man in Search of a Soul, New York, Harcourt, Brace and Company, Inc., 1934.

9. Hoffmann, H.: Familienpsychosen im schizophrenen Erbkreis, Berlin, S. Karger, 1926.

chemical integrations differ in these subjects and may well have something to do with determining deeper regressions.

Much has been written about the body types since Kretschmer's pioneer work. Lewis summarizes this well. He believes that there is evidence to suggest at least that those subjects with the asthenic (leptosome) habitus are psychologically of a schizothymic, introverted, idiotropic make-up, with an abstract, analytic, subjective and suppressed mind and a capacity for schizophrenic disorders. They have a shut-in personality and are given to autistic thinking. In some of the athletic types of subjects and in practically all the dysplastic types dementia praecox tends to develop if the subject becomes psychotic. Therefore, physically the patient with dementia praecox usually exhibits the morphology of one of these three types, although there are many mixtures of the morphologic and personality elements which allow for the arrangement of clinical subgrouping. The pyknic type, as described by Kretschmer, constitutes a large group, which contrasts with the asthenic type and is found chiefly in those in whom manic-depressive psychosis develops.

From anatomic studies at the autopsy table and microscopic examination thereafter little has been learned to elucidate the etiology of dementia praecox. Most of the histologic changes described can be explained as secondary and not causative. Lewis believes that general sclerosis of all the gonads and all the endocrine glands is significant. Also he finds a degree of vascular hypoplasia. A more convincing type of lesion is described by Elvidge,[10] who made repeated biopsies of the brains of a series of schizophrenic patients and observed changes in the oligodendroglia which seemed to run somewhat parallel to the symptom picture.

Physiologic observations have been many and varied. Whitehorn's [11] cardiochronographic records are of great interest because they indicate that the psychotic patient, although he may show superficial signs of emotion, may not show any significant change in the heart rate, whereas a psychoneurotic patient will have a great change of heart rate with emotion but may show little or no outward signs of this. The normal control group lay between these two extremes. In other words, schizophrenia and neurosis are unlike ways of reacting. The neurotic patient seems to overreact with his autonomic system, while the psychotic patient seems to have lost his ability to react adequately with this mechanism. Gildea's [12] work on blood sugar bears out this general

10. Elvidge: Tr. Am. Neurol. A., to be published.

11. Whitehorn, J. C., and Richter, H.: The Unsteadiness of the Heart Rate in Psychotic and Neurotic States, Arch. Neurol. & Psychiat., to be published.

12. Gildea, E. F.; Mailhouse, V. L., and Morris, D. P.: Am. J. Psychiat. **92**:115, 1935.

idea, for normal subjects in a state of fear show hyperglycemia, while psychotic patients who exhibit all the symptoms of fear may show no change in the blood.

Fischer's early work, which showed that many patients with schizophrenia have a low basal metabolic rate and a decrease in the specific dynamic action of protein, has been followed by a great deal of physiologic observations, principally at two centers of research, the Elgin State Hospital, in Illinois, and the Worcester State Hospital, in Massachusetts. At the former Finkelman and Stephens found among other phenomena a low production of heat in response to cold—a dissociation between the appreciation of cold and the defense mechanisms—and no reactive hyperthermia in a group of fifty patients with hebephrenic dementia praecox. They conclude that the disturbance in heat regulation in dementia praecox is probably due to some physiologic condition in the hypothalamus.

Hoskins and his group of investigators [13] found that many schizophrenic patients had a depressed metabolism, but more conspicuous was a tendency to abnormal variability in many bodily functions: urinary constituents, output of urine, blood flow, blood count and blood sugar. The averages of the observations were usually within normal limits, but "nearly all of the functions studied showed a high individual variability." There seems to be a lack of homeostasis.

The results of none of these investigations are particularly striking, but the combined material, so carefully abstracted and put together by Lewis, brings home the conclusion that here in the study of schizophrenia the modern point of view is essential and is bearing fruit. Workers no longer have to waste time over discussions as to whether the disturbance is mental or physical. The soma and the psyche make a working unit. Abnormality in either one may cause disorganization and may precipitate symptoms in a susceptible organism. As Eddington says: "We often think that when we have completed our study of *one* we know all about *two* because two is *one and one;* we forget that we have still to make a study of *and*—that is to say of organization."

That certain persons are more susceptible to schizophrenia than others is obvious from the studies on constitution and inheritance, but it seems likely that only those who show extreme involvement, the patients with the worst "stuff" in them, of necessity will later have dementia praecox. Innumerable persons in the community inherit the tendency, are "that sort of person," but with proper hygiene, mental and physical, can live useful and productive lives. Campbell [14] presents the mental

13. Hoskins, cited by Lewis,[7] chap. 4.

14. Campbell, C. M.: Destiny and Disease in Mental Disorders, New York, W. W. Norton & Company, Inc., 1935.

aspects of the subject in a most convincing way in his Salmon lectures, especially in the chapter entitled "Our Kinship with the Schizophrenic."

Therapy is most varied. Skalweit [15] discusses various methods that have been tried, ranging from causing a patient to have convulsions by injecting camphor (!) to various glandular treatments—total ovary and insulin being the newest.[16] For a disturbed and excited patient a combination of bulbocapnine and scopolamine seems to work well. Psychoanalysis is used with various results in cases in which the symptoms are mild. All one can say at present is that each patient must be studied individually from all angles, and then a regimen must be instituted which may give more stability to both the internal and the external environment.

BLOOD

In the section on schizophrenia some of the changes in the constituents of the blood in relation to behavior have been discussed. A great deal of work has been carried on for years along these lines, and little has appeared in the way of tangible results. Gildea's observations (previously discussed) are important, in that they indicate that normal subjects show a rise in the sugar content of the blood more easily than psychotic patients. Diethelm [17] reports observations by means of the dextrose tolerance test which indicate that anxiety, panic and tension may cause a striking rise in the sugar tolerance curve. For example, when at ease a woman with phobias showed the following dextrose tolerance curve:

97 (before dextrose)—151, 132, 94 and 86 mg.

In a fearful situation three days later the curve was as follows:

110 (before dextrose)—165, 153, 86 and 106 mg.

Another patient, who was tense and stammered, before being made to telephone and stammer badly showed the following curve:

83 (before dextrose)—149, 156, 122 and 77 mg.

After acute stammering the curve was as follows:

102 (before dextrose)—163, 171, 123 and 98 mg.

He discusses twenty-six cases and wisely warns that it is difficult to evaluate critically the emotional factors, for the depth and acuteness of emotional responses cannot be judged by the outward display even of normal subjects.

As regards a relationship between the lipoid content of the blood serum and the body build, Gildea, Kahn and Man [18] have done an

15. Skalweit, W.: Fortschr. d. Neurol., Psychiat. **8**:256, 1936.

16. Benedek, L.: Insulin-Schock-Wirkung auf die Wahrnehmung, Berlin, S. Karger, 1935.

17. Diethelm, O.: Influence of Emotions on Dextrose Tolerance, Arch. Neurol. & Psychiat. **36**:342 (Aug.) 1936.

18. Gildea, E. F.; Kahn, E., and Man, E. B.: Am. J. Psychiat. **92**:1247, 1936.

important piece of work. Men in good health were selected from a university community on the basis of their close conformity with one extreme or the other of a bipolar classification of body build. The subjects who corresponded in most respects to Kretschmer's description of the pyknic in physique represented one extreme, and the slender subjects, the leptosomes, the other extreme. It was found that the lipoid content of the serum (total fatty acids and cholesterol) was consistently higher in the seventeen men of pyknic body build than in the twenty-four men of leptosomic physique. The difference between the total fatty acid content of the pyknic and that of the leptosomatic subjects was marked, being eight and seven-tenths times as large as the probable error of the difference. A pyknic body build, a high output of energy and high lipoid values were considered as pyknophilic factors. A leptosomic body build, a low output of energy and low lipoid values were considered leptophilic factors. These findings suggest that a relationship exists among at least three of the morphologic, biochemical and functional factors that make up the person who represents a relatively pure form of either the pyknic or the leptosomic physique.

HYPOTHALAMUS

It has been known for many years that lesions in the nuclei about the third ventricle, below the thalamus, cause somnolence in man. It has now been shown that these lesions in animals (cats and monkeys) will do the same. Moreover, stimulation of this part of the brain sets up a complex reaction pattern characteristic of intense emotion: rapid respiration, dilatation of the pupils, erection of hair and constriction of blood vessels. It has been observed also that after the removal of the cerebral hemisphere and thalamus of a cat, leaving the hypothalamus intact, the animal is subject to great fits of rage. If, however, the hypothalamus is injured, this rage reaction is lost. Thus there seems to be a center in the hypothalamic region where emotional reactions are integrated and where vegetative functions are controlled. The nuclei in question are located at the transition of the forebrain into the midbrain. There are ten pairs of nuclei closely related anatomically, the more important of which are the supra-optic, paraventricular, mamillary and tuberomamillary nuclei. Ranson and his co-workers [19] have been doing much careful work along anatomic and physiologic lines, which

19. (*a*) Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935. (*b*) Ingram, W. R.; Hannet, F. I., and Ranson, S. W.: J. Comp. Neurol. **55**:333, 1932. (*c*) Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain: The Resultant Alterations in Blood Pressure, Arch. Neurol. & Psychiat. **34**:931 (Nov.) 1935.

has added greatly to the exact knowledge of this important region. Not only have they produced the aforementioned symptoms, but they have found a well localized point in the lateral hypothalamic area stimulation of which causes a rise in blood pressure.

Clinicians have not been backward in taking up the lead, and now a great many syndromes are described as due to hypothalamic lesions. Lhermitte [20] enumerates diabetes insipidus, narcolepsy, hyperorexia, glycosuria, lipodystrophy, retinitis pigmentosa and adiposogenital dystrophy and adds others that are less well substantiated. Obviously much more needs to be learned. So many and so varied functions cannot be controlled in so small an area. The probability is that the hypothalamus is one of several regions where vegetative nuclei are clustered and where integration of vegetative function takes place. All important functions are controlled from several levels of integration.

Bearing on this is the recent work from Fulton's laboratory. Kennard [21] extirpated various parts of the cerebral cortex in monkeys and found that lesions in area 6a of the frontal lobe caused cooling of the contralateral side of the body, a diminution of sweat and sometimes edema. Kabat, Magoun and Ranson [19c] found an area in the frontal lobe of cats electrical stimulation of which caused a fall in blood pressure. Some single clinical cases have been reported which give evidence of a similar nature, but the recent paper by Ellis and Weiss [22] reports a study of thirty-five patients with hemiplegia, all of whom had a greater blood flow in the paralyzed arm than in the normal arm; thirteen showed edema of the affected hand. Three patients came to autopsy and showed lesions affecting cortical cells or fibers but not the hypothalamus. There is accumulating good evidence, therefore, that the autonomic nervous system is far from being merely peripheral and automatic but has controlling centers even in the cerebral cortex.

PSYCHONEUROSIS

Ross [23] has just written an important book entitled "Prognosis in the Neuroses." He reports on the results of treatment at the Cassel Hospital for Functional Nervous Disorders, at Penshurst, Kent, since 1920. Before discussing the data he critically evaluates the possible errors and discusses the probable fallacies, coming to his conclusion cautiously and intelligently.

20. Lhermitte, J.: Rev. neurol. **1**:809, 1934.

21. Kennard, M. A.: Vasomotor Disturbances Resulting from Cortical Lesions, Arch. Neurol. & Psychiat. **33**:537 (March) 1935.

22. Ellis, L. B., and Weiss, S.: Vasomotor Disturbance and Edema Associated with Cerebral Hemiplegia, Arch. Neurol. & Psychiat. **36**:362 (Aug.) 1936.

23. Ross, T. A.: An Enquiry into Prognosis in the Neuroses, London, Cambridge University Press, 1936.

Three methods of psychotherapy were employed at the hospital —hypnotism, persuasion and analysis. Hypnotism was used only occasionally. "On the whole it is probable that it affects the prognosis adversely: it does not tend to enable the patient to stand on his own feet. No one who has used it doubts its immediate potency, but that is of little importance." Persuasion connotes not suggestion but a more educational process. A long history is taken that eventually brings up forgotten things; a meticulous examination is carried out, and it is demonstrated to the patient that most of his symptoms commonly accompany emotion in everybody. It is then pointed out that the methods of management of his life in the past were bad. After this, in many instances, the symptoms disappear.

Analysis, as the term is used by Ross, is not the regular freudian procedure but an eclectic application of psychologic methods for studying each patient individually. "Our belief was largely in an individual psychology, i. e., that the patient's personal experience was the important thing; some of this when he came under observation was conscious, some of it had become unconscious; we were interested also in trends which had not yet become experience, and often not yet conscious. What we aimed at was to discover what experiences an individual had encountered and how they had affected him. Much of this is often repressed, and the exploring of such repressions is frequently, as it seems to me, of more value than following the development of the infantile mind through the various stages which have been described by the Freudians, but which were possibly invented by them."

Besides these forms of therapy there were general medical supervision, contact with other patients with all its educational implications, occupational therapy, work and organized games.

In these ways 1,186 patients were treated between 1920 and 1934. Reports one year after discharge showed 45 per cent well, 25 per cent improved and 19 per cent not benefited. Reports after three years were not quite so good: 40 per cent well and 10 per cent improved, but there were many more "lost sight of"; after five years 34 per cent were well and 6 per cent were improved, the falling off probably being partly due to losing track of the patients. Special groups are discussed. The obsessional and compulsive neuroses seem to be the most difficult to treat. Concerning traumatic neurosis, he wisely remarks: "If the legal profession, bench, bar and solicitors, could grasp the conception of neurosis, and if it were possible that legislators could become capable of being educated to see that not trauma, but advantage to be gained by a history of trauma, was what made these people ill, this form of illness would disappear." Among alcoholic subjects he finds that homosexuality plays a considerable rôle.

Freud's[24] "Autobiography" is another milestone in the psychoanalytic field. The historical sketch of psychoanalysis is one of the best expositions extant of what it really is all about. For instance, in chapter 3 he says: "The theory of repression became the foundation-stone of our understanding of the neuroses. . . . the task of therapy. . . . as to uncover repressions and replace them by acts of of judgment." Again in chapter 4 he says: "The theories of resistance and of repression, of the unconscious, of the etiological significance of sexual life and of the importance of infantile experiences—these form the principal constituents of the theoretical structure of psychoanalysis." And "What poets and students of human nature had always asserted turned out to be true: the impressions of that remote period of life, though they were for the most part buried in amnesia, left ineradicable traces upon the individual's growth and in particular laid the foundations of any nervous disorder that was to follow. But since these experiences of childhood were always concerned with sexual excitations and the reaction against them, I found myself faced by the fact of infantile sexuality—once again a novelty and a contradiction of one of the strongest of human prejudices." In this last passage crops up again what I have criticized before, the use of such unscientific words as any and always, but in this autobiography one can find the main theories expressed simply and clearly.

In May of this year was celebrated the eightieth birthday of Sigmund Freud. It is interesting that the principal speaker at the Vienna occasion was an artist, Thomas Mann,[25] who explained how much the freudian theory has illuminated literature and explained philosophic concepts like those of Schopenhauer. He feels that psychoanalysis has brought a healthy skepticism into the world "which unmasks all the schemes and subterfuge of our own souls." Freud once called his theory of dreams "a bit of scientific new-found-land won from superstition and mysticism." The address is interesting reading, it shows how widely the freudian doctrines have spread; it is not so much what Thomas Mann says as the fact that he says it!

24. Freud, S.: Autobiography, translated by J. Strachey, ed. 2, New York, W. W. Norton & Company, Inc., 1935.

25. Mann, T.: Life and Letters Today **15**:80, 1936.

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Book Reviews

Medical Papers. Dedicated to Henry Asbury Christian, Physician and Teacher. From his Present and Past Associates and House Officers at the Peter Bent Brigham Hospital, Boston, Massachusetts. Price, $10. Pp. 1,000. Baltimore: Waverly Press, 1936.

This handsome volume contains no less than a hundred contributions by students and associates, past and present, of Dr. Christian, published in celebration of his sixtieth birthday. The reviewer has seen few *Festschrifte* more imposing and none which conveys a stronger impression of love and respect on the part of those who have joined in a tribute to their friend and teacher. The reviewer, though not directly associated with Dr. Christian, takes this opportunity to add his inarticulate homage to a man who has always stood for the best in American medicine—sound practice, unswerving search for the truth and stimulating guidance of students and associates. Dr. Christian has achieved the rare privilege of becoming, like Shattuck, Osler and Thayer, a tradition in his own lifetime. The subjects of the various essays show, as one might expect, a wide range of interests. It is not possible to go into detail here, but almost every phase of internal medicine is touched on. Some of the work comes from the laboratory, and at the other extreme is a pleasant sprinkling of philosophic essays dealing with medical practice and teaching. Finally, the register of the former and the present members of the medical staff of the Peter Bent Brigham Hospital adds a note of biographic interest.

Traité de physiologie normale et pathologique. Edited by G. H. Roger and L. Binet. **Volume X. Physiologie nerveuse (deuxième partie).** Fascicles 1 and 2. Price, 250 francs. Pp. 981, with 275 illustrations. Paris: Masson & Cie, 1935.

The appearance of this work completes the first volume. Volume IX, which was published in 1933, also dealt with the nervous system.

The work is primarily one of reference for French students of medicine. It reviews in some detail the more important features of physiology, with considerable attention to the historical background. The volumes are far from complete, however, in their presentation and are evidently not intended for the specialist, except in a few instances in which the sections are written by persons preeminent by virtue of important contributions to the subject.

Elektrokardiographische Befunde bei Herzinfarkt. By Anton Jervell. Pp. 267, with 112 illustrations. Oslo: Kirstes Boktrykkeri, 1935.

This book is a reprint of an article in *Acta Medica Scandinavica*, written by Dr. Anton Jervell, first assistant in Professor Müller's clinic in Oslo. Electrocardiographic-minded physicians will appreciate it.

In brief, Jervell describes the electrocardiographic findings which he observed in a series of sixty-five patients with coronary thrombosis, thirty-six of whom were followed up to section. The book is attractively arranged; the reports of the cases are short and to the point, and the illustrations, which comprise tracings and diagrams of the heart, are admirably clear. A bibliography of two hundred and seventy-two references to the recent literature on coronary thrombosis concludes the volume. On the whole, this monograph represents excellent workmanship and is an admirable contribution to the subject of cardiovascular disease.

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